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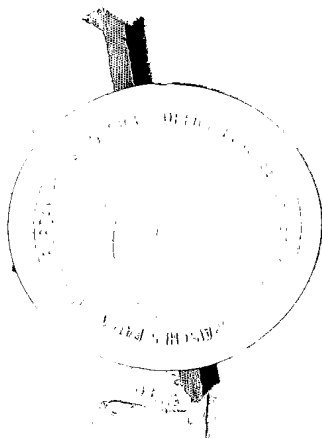
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## COMPOSITION OF PROTEIN COMPLEXES ASSOCIATED WITH THE PROCESSING OF APP AND THE A $\beta$ -PEPTIDES

### 1. FIELD OF THE INVENTION

The present invention relates to protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

### 2. BACKGROUND OF THE INVENTION (references are listed in supra)

Alzheimer's disease is a chronic condition that affects millions of individuals worldwide. After onset of the disease sufferers require a high degree of supervision and care. As the proportion of aged individuals in the population increases, the number of sufferers of Alzheimer's disease is expected to expand dramatically. Current top drugs (e.g. Aricept®/donepezil) attempt to achieve a temporary improvement of cognitive functions by inhibiting acetylcholinesterase, which results in increased levels of the neurotransmitter acetylcholine in the brain. These therapies are not suitable for later stages of the disease, they do not treat the underlying disease pathology, and they do not halt disease progression. The growing need for an effective therapy, coupled with the absence of effective treatments, presents a significant opportunity for drug target development and drug discovery.

The brains of sufferers of Alzheimer's disease show a characteristic pathology of prominent neuropathologic lesions, such as the initially intracellular neurofibrillary tangles (NFTs), and the extracellular amyloid-rich senile plaques. These lesions are associated with massive loss of populations of CNS neurons and their progression accompanies the clinical dementia associated with AD. The major component of amyloid plaques is the amyloid beta peptide. Amyloid beta is the proteolytic product of a precursor protein, beta amyloid precursor protein (beta-APP or APP). APP is a type-I trans-membrane protein which is cleaved by several different membrane-associated proteases. The first cleavage of APP occurs extracellularly by one of two proteases, alpha-secretase or beta-secretase. Beta-secretase or BACE1 (beta-site APP-cleaving enzyme) is a type-I

transmembrane protein containing an aspartyl protease activity (described in detail below). Alpha secretase is a metalloprotease whose activity is most likely to be provided by one or a combination of the proteins ADAM10 and ADAM17. Following either the beta or alpha cleavage of APP, the final cleavage event occurs within the membrane and is carried out by a protein complex called gamma secretase. It is the combination of the beta and gamma secretase activities that results in the liberation of the Abeta peptides of 40 and 42 residues (there are also lower levels of other forms) from the APP and ultimately the formation of the amyloid plaques responsible for the pathology of Alzheimer's disease. It is believed that the Abeta-42 peptide is the most critical Abeta species, because it shows the most pronounced neurotoxicity, and can aggregate easily, thus forming a nucleus for the aggregation of other Abeta peptides, such as the Abeta-40 which is typically produced at higher levels than the other species.

The applicant's proprietary proteomics technology (TAP/LC-MS/MS) is particularly successful in the elucidation of membrane protein complexes. These multiprotein complexes form the core of the APP processing pathway and are not amenable to other techniques. Known proteins with an important functional role in APP processing were analysed with The applicant's technology to comprehensively chart the dynamic protein interactions that contribute to Abeta production. Selected novel targets are subsequently validated using cellular or biochemical assays. Moreover, purified multi-protein complexes (e.g. beta- or gamma-secretase) do represent defined functional molecular machines, which are used to evaluate the mechanism of known compounds and for the optimisation of leads.

#### **APP intracellular domain (AICD) (AICD) (APP intracellular domain (AICD) (AICD))**

The cytoplasmic tail of APP is liberated into the cytoplasm by gamma-secretase cleavage of either the alpha- or beta-C-terminal transmembrane fragment (1). Cao and Sudhof (2) showed that the cytoplasmic tail of APP forms a complex with the nuclear adaptor protein Fe65 and the histone acetyltransferase TIP60. This complex stimulates transcription via heterologous Gal4 or LexA DNA binding domains, suggesting a function of the APP intracellular domain (AICD) in gene expression, analogous to what has been described for the Notch intracellular domain (3). Recent reports suggest that a complex

formed by the APP intracellular domain (AICD) and associated proteins could modify expression of genes that function in inflammation (4) or apoptosis (5). Hence, novel proteins associated with the cytoplasmic and nuclear complexes of the APP intracellular domain (AICD) that regulate APP intracellular domain (AICD) stability and turnover, nuclear translocation, and its transcriptional function, are potential targets for therapeutic intervention.

## **BACE2**

BACE2 is a glycosylated transmembrane protein of the aspartic protease family, constitutes the only paralog of BACE1, and was mapped to the Down's critical region of human chromosome (6-9). Both endoproteases share similar structural organization including a prodomain, a catalytic domain formed via DTG and DSG active site motifs, a single transmembrane domain, and a short C-terminal tail. BACE2 is expressed at low levels in most human peripheral tissues and at higher levels in colon, kidney, pancreas, placenta, prostate, stomach, and trachea. Human adult and fetal whole brain and most adult brain subregions express very low or undetectable levels of BACE2 mRNA (10). BACE2 has a limited effect on the beta-secretase site but efficiently cleaves the sequences near the alpha-secretase site (11). BACE2 localizes in the endoplasmic reticulum, Golgi, trans-Golgi network, endosomes, and plasma membrane, and its cellular localization patterns depend on the presence of its transmembrane domain. BACE1 knockout mice are viable, possibly due to a redundancy in function with BACE2 (12).

Protein complexes involving BACE2 are of potential therapeutic value in AD therapy. The determination of the nature of the proteins interacting with and potentially regulating BACE1 but not BACE2 will constitute suitable therapeutic targets.

## **BRI**

Familial British dementia (FBD) is a neurodegenerative disease characterised by pathological hallmarks that are strikingly similar to AD, including amyloid fibrils and neurofibrillary tangles (13). However the fibrils in FBD are not formed by amyloid-beta peptides as in AD, but from a unique 4-kD protein subunit, called ABRI, that is encoded by a novel gene, BRI (13). The BRI cDNA encodes a protein of 266 amino acids with a

putative single transmembrane-spanning domain between amino acids 52 and 74, indicating that this highly insoluble molecule is a type II integral transmembrane protein with the C-terminal part being extracellular. A potential N-glycosylation site was identified at asp-170. In the disease, a single base substitution at the stop codon of the BRI gene results in a larger, 277-residue precursor, BRI-L. Release of the 34 carboxy-terminal amino acids from the mutated precursor generates the ABri amyloid subunit. It has been reported that both BRI-L and wild-type BRI were constitutively processed by the proprotein convertase, furin, resulting in the secretion of carboxyl-terminal peptides that encompass all or part of Abri (14).

The protein complex around BRI is of high potential therapeutic interest for AD and related neurodegenerative diseases because BRI pathology leads to very similar downstream pathological effects like tangle formation, and hence could provide molecular links between amyloid formation and intracellular pathways eventually leading to tau phosphorylation and tangle buildup.

### **Dab1**

We have used mouse DAB1 because human Dab1 has not been cloned. Mutation in disabled-1 (Dab1) resemble mutations in reelin (Reln) by causing abnormalities in laminar structures throughout the brain and ataxia in reeler and scrambler mice (15). However, Reln and Dab1 are distinct in their molecular properties. Reln is a large extracellular protein secreted in the forebrain and the cerebellum. Dab1 is a cytoplasmic adapter protein that functions in phosphorylation-dependent intracellular signal transduction. It is suggested that Dab1 functions downstream of Reln in a signaling pathway that controls cell positioning in the developing brain (15). Reelin stimulates tyrosine kinases of the src family by a mechanism involving Dab1 (16). DAB1 has also been reported to interact with APP (17) and with the cytoplasmic tails of LRP and LDL receptor (18). It was shown that Reln binds directly and specifically to the extracellular domains of VLDLR and ApoER2. Blockade of VLDLR and ApoER2 ligand binding correlated with loss of Reelin-induced Dab1 tyrosine phosphorylation. Mice lacking either Reln or VLDLR and ApoER2 show an increase in the phosphorylation level of tau proteins suggesting that Reln acts via Vldlr and ApoER2 to regulate Dab1 tyrosine

phosphorylation and tau function in neurons (18). The functional role of the binding of Dab1 to the C-termini of APP, APLP1 and APLP2 has not been elucidated.

The protein complex around DAB1 is of high potential therapeutic interest for AD and related neurodegenerative diseases because it could provide further links of amyloid pathology to downstream tangle pathology, and provide targets for the therapeutic modulation of the intracellular pathways leading to tau phosphorylation, tangle buildup, and neuronal death in AD.

### **Fe65L2**

Fe65 proteins are ligands of the cytoplasmic domain of APP (1). The fe65 gene has two paralogues, Fe65L1 (19) and Fe65L2 (20). Fe65L2 encodes a protein of approx. 50 kDa which is expressed predominantly in brain and testis (21). The three paralogues of the Fe65 protein family share three regions corresponding to the protein-protein interaction domains; the WW domain and the two PTB domains, whereas the remaining sequences are poorly related. Like Fe65, Fe65L1 and Fe65L2 genes encode two different protein isoforms, derived from the alternative splicing of a six nucleotide exon within the N-terminal PTB domain, in the presence or absence of two acidic/basic amino acids. Fe65 proteins have been found to translocate into the nucleus and to prevent the activation of the thymidylate synthase gene promoter induced by the transcription factor CP2 by an unknown mechanism (22).

Fe65L2 is able to interact, both in vitro and in vivo, with the intracellular domain of APP. Fe65 and Fe65L2 interact with APP, APLP1 and APLP2 with different efficiencies (20). Overexpression of Fe65L2 was reported to increase secretion of Abeta 1-40 and Abeta 1-42, however the molecular mechanism of this amyloidogenic effect is unknown. A c954C-->T polymorphism in the Fe65L2 gene is possibly associated with early-onset Alzheimer's disease (21). Fe65 proteins have been found to translocate into the nucleus and to prevent the activation of the thymidylate synthase gene promoter induced by the transcription factor CP2 by an unknown mechanism (22). There are no interactors of Fe65L2 known that are not also found with Fe65.

The protein complex around Fe65L2 is of high potential therapeutic interest for AD and related neurodegenerative diseases because membrane-associated, cytoplasmic and nuclear complexes of the APP intracellular domain (AICD) with adaptor

proteins regulate APP stability and turnover, nuclear translocation, and its transcriptional function, which are all potential targets for therapeutic intervention.

### **Pilt/TJP4**

Pilt, also termed TJP4, was cloned as a novel tight junction protein that contains coiled-coils and a proline-rich domain (23). It binds to hDlg. X11 is a negative regulator of Abeta secretion.

Pilt is a novel interactor of X11beta. Novel proteins associated with X11beta and Pilt could regulate APP turnover and processing and APP intracellular domain (AICD) dependent gene expression, and hence are potential targets for therapeutic intervention.

### **Paladin**

Paladin is a novel protein tyrosine phosphatase. The physiological role, subcellular localisation, substrates, and interacting proteins are unknown.

In addition to the predicted PTP domain, there is a second less perfectly conserved PTP domain. Part of other sequence regions are also duplicated. Paladin could bridge dimers of X11 and APP. Paladin is a novel interactor of X11beta and the C-terminus of APP.

Novel proteins associated with X11beta and the C-terminus of APP could regulate APP turnover and processing and APP intracellular domain (AICD) dependent gene expression, and hence are potential targets for therapeutic intervention (e.g. paladin-specific phosphatase inhibitors).

### **Neurotrypsin**

Neurotrypsin is a mosaic protein of 761 aa consisting of a kringle domain, followed by three scavenger receptor cysteine-rich repeats, and a serine protease domain (24-27). The protease domain belongs to the subfamily of trypsin-like serine proteases. The exact function of the protease and its mechanism of action is unknown. There are no interacting proteins known. Expression of neurotrypsin in the adult murine nervous system is confined to distinct subsets of neurons. The most prominent expression was

found in the cerebral cortex, the hippocampus, and the amygdala, ie structures engaged in the processing and storage of learned behaviors and memories (24). Together with the recently obtained evidence that extracellular serine proteases play a role in neural plasticity, this expression pattern suggests that the extracellular proteolytic action of neurotrypsin subserves structural reorganizations associated with learning and memory operations (24). The developmental expression pattern in the mouse embryo suggests roles of neurotrypsin in morphogenesis of nonneural tissues, as well as in neural development, in particular in axonal target invasion, synaptogenesis, and Schwann cell differentiation (28). A 4-base pair deletion in the neurotrypsin gene is associated with autosomal recessive nonsyndromic mental retardation (MR). Immuno-electron microscopy on adult human brain sections revealed that neurotrypsin is located in presynaptic nerve endings, particularly over the presynaptic membrane lining the synaptic cleft suggesting that neurotrypsin-mediated proteolysis is required for synaptic function and defects in neurotrypsin function may cause mental retardation (29). Neurotrypsin and novel proteases associated with it may regulate Abeta secretion through BACE- and gamma-secretase dependent processing. Alternatively, Neurotrypsin may cleave APP and Abeta peptides directly. Note that APP is also localised at presynaptic nerve endings, consistent with a role of Neurotrypsin in APP processing. Neurotrypsin, its interacting proteins, and in particular its protease activity are therapeutic targets for neurodegenerative disease characterised by Abeta pathology.

### **Hunc-18 (Syntaxin-binding protein 1)**

Hunc18a is the human ortholog of mouse Munc18a, an SM-protein that is essential for neurotransmitter release (30). It has been suggested that binding of Hunc18a to syntaxins 1a, 1b, 2 and/or 3 is required for its fusogenic function (31). Recently, a synergistic effect of Hunc18a and X11 proteins on amyloid precursor protein metabolism has been demonstrated. The molecular mechanism underlying this phenomenon is, however, not understood. However, it appears to be independent of a direct interaction of Munc18a with X11 (32).

Novel proteins associated with Hunc18a and X11 complexes are potential targets for therapeutic intervention.

### **Telencephalin**



Telencephalin is a member of the intercellular adhesion molecule (ICAM) family, type I transmembrane glycoproteins, that contain 2-9 immunoglobulin-like C2-type domains, and bind to the leukocyte adhesion LFA-1 protein (33,34). This protein is expressed on the surface of telencephalic neurons and displays two types of adhesion activity, homophilic binding between neurons and heterophilic binding between neurons and leukocytes. It may be a critical component in neuron-microglial cell interactions in the course of normal development or as part of neurodegenerative diseases (35).

The C terminus of PS1 and PS2 binds to the telencephalin (TLN) in the brain (35). PS1 deficiency results in the abnormal accumulation of TLN in a yet unidentified intracellular compartment. The first transmembrane domain and carboxyl terminus of PS1 form a binding pocket with the transmembrane domain of TLN suggesting that a telencephalin-containing protein complex be involved in the pathogenesis of Alzheimer's disease (35).

Novel proteins associated with telencephalin and gamma-secretase complexes are potential targets for therapeutic intervention..

## **PC7**

PC7 is a a furin-like prohormone convertase that contains a 42-residue signal peptide at the N terminus, 6 potential N-linked glycosylation sites, and a 22-amino acid transmembrane region (36). It shares more than 50% amino acid identity over the catalytic region with other members of the prohormone convertase family and is structurally more closely related to PACE and PACE4 than to PC1 or PC2.

Because activation of BACE is believed to be performed by furin, but not by PC7, and activation of ADAM10 can be induced by both PC7 and furin, the competition between BACE and ADAM10 with regard to APP cleavage might be shifted to the nonamyloidogenic pathway by an inhibition of furin and/or a simultaneous stimulation of PC7. Considering the resemblance between PC7 and furin, this might be difficult to achieve. However, pathways that lead to enhanced gene expression of PC7 may be beneficial in the cause of AD (37,38).

Hence, novel proteins associated with PC7 protein complexes, in particular PC7 substrates, are potential targets for therapeutic intervention.

## **TFCP2**

Lambert et al. (2000) described an association between a noncoding polymorphism (G-A) in the 3' untranslated region of the transcription factor TFCP2 and sporadic Alzheimer disease, suggesting a protective effect (39). The A allele demonstrated reduced binding to nuclear protein(s) from a neuroblastoma cell line, and absence of the A allele was associated with lower gene expression in lymphocytes from AD cases compared with controls. Polymorphisms in TFCP2 may hence be important for the pathogenesis of AD, particularly since the TFCP2 gene product was shown to interact with GSK3B, Fe65, and other factors involved in the inflammatory response (39).

Novel proteins associated with the nuclear complexes of TFCP2 may play a role in the etiology of AD, e.g. in APP intracellular domain (AICD) dependent gene expression, and hence are potential targets for therapeutic intervention.

## **JIP1 (MAPK8IP1)**

The JIP proteins (40) function by scaffolding components of a MAP kinase module (including MLK, MKK7, and JNK) and facilitate signal transmission by the protein kinase cascade (41).

Waeber et al. evaluated the role of JIP1 in beta-cells and proposed JIP-1 as a candidate gene for human diabetes. In one family a JIP1 missense mutation S59N segregated with diabetes and thus JIP1 represents a candidate susceptibility gene for type 2 diabetes (42).

Two groups presented evidence for an interaction of JIP1b with the cytoplasmic tail of APP (43-45). Another group reported a mutual relationship of the expression levels of JIP1 and alpha synuclein in cultured neurons (46). Over-expression of JIP1 has been reported to stabilize immature APP and to suppress the production of an intracellular carboxyl-terminal fragment of APP (APP intracellular domain (AICD)), and the secretion of peptides A-beta 1-40 and A-beta 1-42, the predominant constituents of amyloid plaques in Alzheimer's disease. The mechanism of JIP1's amyloidogenic function is unknown. JIP1 and related proteins JIP2 and JIP3 bind to the C-terminus of kinesin light

chain suggesting that a JIP1-containing protein complex might be involved in APP trafficking (47,48).

The protein complex around JIP1 is of high potential therapeutic interest for AD and related neurodegenerative diseases because membrane-associated, cytoplasmic and nuclear complexes of the APP intracellular domain (AICD) with adaptor proteins regulate APP stability and turnover, nuclear translocation, and its transcriptional function, which are all potential targets for therapeutic intervention.

### **FKRP**

Brockington et al. identified the fukutin-related protein gene (FKRP) by database screening using the mouse fukutin sequence and cloned fukutin-related protein (FKRP) by a combination of EST assembly, RT-PCR, and RACE (49). The cDNA encodes a 495-amino acid protein with a molecular organization similar to several Golgi-resident glycosyltransferases. Northern blot analysis detected a 4.0-kb FKRP transcript expressed predominantly in skeletal muscle, placenta, and heart and relatively weakly in other tissues.

FKRP mutations are found in families with severe and early-onset phenotypes of congenital muscular dystrophies (CMD). Structural brain defects, with or without mental retardation, are additional features of CMD. A variable reduction of alpha-dystroglycan expression was observed in the skeletal muscle biopsy of all individuals studied. In addition, several cases showed a deficiency of laminin 2 (49,50).

FKRP and fukutin are Golgi-resident proteins and FKRP is required for the post-translational modification of dystroglycan (51).

FKRP is a novel interactor of PS1. Since exit of presenilins and the active gamma-secretase complex from the ER is critical for gamma-secretase function (52), FKRP and associated proteins may play a role in regulating gamma-secretase activity and/or trafficking, allowing access to APP. Interfering with FKRP and associated proteins may be a therapeutic strategy for the treatment of AD.

### **VTRP**

VTRP is a putative transport-related protein that was originally cloned from cultured astrocytes. It is an immediate-early gene expression of which is induced 15 min

after reoxygenation(following an episode of hypoxia (53). There are no interacting proteins known.

SLY1, a member of the evolutionarily conserved Sec1/Munc-18 family of proteins, is an essential gene for vesicular transport between the ER and the cis Golgi in *S. cerevisiae*. Analogously, interaction of rat Sly1 (which is 95% identical with human VTRP) with syntaxins 5 and 18 serves an important function in regulating intracellular traffic in vertebrates (54).

Since exit of presenilins and the active gamma-secretase complex from the ER is critical for gamma-secretase function (52), VTRP and associated proteins might play a role in regulating gamma-secretase activity. Interfering with VTRP regulated trafficking events may be a therapeutic strategy for the treatment of AD.

### 3. SUMMARY OF THE INVENTION

An object of the present invention was to identify protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the protein complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said complexes were identified. The components are listed in table 1.

Said object is further achieved by the characterization of component proteins. These proteins are listed in table 2.

Thus, the invention relates to the following embodiments:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and

(b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. A protein complex comprising a first protein selected from the proteins listed in table 1, fourth column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
3. A protein complex comprising all proteins selected from the proteins in table 1, third column of a given complex or at least one protein being a homologue thereof, or a variant thereof or functionally active fragment or functionally active derivative of said

protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions;

wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or at least one protein being a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, except at least one protein of the proteins listed in table 5, third column, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, with the proviso that the complex comprises at least one protein selected from table 1, fifth column of a given complex.
5. The complex of any of No. 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in at least one biochemical activity as stated in table 3.
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the protein, preferably the tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of a protein complex obtainable by a process according to any of No. 9 - 11.
13. Protein selected from the group of proteins in table 1, sixth column of a given complex or a homologue or a variant of thereof, or a functionally active fragment or a functionally active derivative of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to No. 13.
15. Construct, preferably a vector construct, comprising
  - (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
  - (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, being selected from the second group of proteins according to No. 1 (b) or
  - (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.
16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and /or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid encoding at least one protein selected from the first group of proteins according to No. 1 (a) and at least one nucleic acid encoding at least one protein selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody containing the binding domain thereof which binds to any of the proteins of the group of proteins according to No. 13.
18. A kit comprising in one or more containers:
  - (a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or
  - (b) an antibody according to No. 17 and/or
  - (c) a nucleic acid encoding a protein of the complex of any of No. 1 - 8 and/or a protein of No. 13 and/or



- (d) cells expressing the complex of any of No. 1 – 8 and/or a protein of No. 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to No. 18 for processing a substrate of a complex of any one of No. 1 - 8.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as those as stated in column 2, table 4 of a given complex.
21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 13 and/or at least one antibody according to No. 17 is attached to a solid carrier.
22. A process for modifying a substrate of a complex of any one of No. 1 - 8 comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.
23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or a protein according to No. 13.
24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders, preferentially for diseases or disorders such as those as stated in column 2, table 4 of a given complex.
25. A method for screening for a molecule that binds to a complex of any one of No. 1 - 8 and/or a protein of No. 13, comprising the following steps:
  - (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:
- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.
27. The method of No. 26, wherein the amount of said complex is determined.
28. The method of No. 26, wherein the activity of said complex is determined.
29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.

31. The method of No. 30, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as those as stated in column 2, table 4 of a given complex.
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as those as stated in column 2, table 4 of a given complex.
34. A method for the production of a pharmaceutical composition comprising carrying out the method of No. 26 - 31 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.
40. The method of No. 39, wherein said determining step comprises determining whether any of the proteins according to No. 13 is present in the complex.
41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment thereof of No. 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as those as stated in column 2, table 4 of a given complex.
42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity of, or protein composition of, said complex.
43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of No. 1 - 8 and/or a protein as listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target, in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as a neurodegenerative disease such as those as stated in column 2, table 4 of a given complex.

### 3.1 DEFINITIONS

The term "activity" as used herein, refers to the function of a molecule in its broadest sense. It generally includes, but is not limited to, biological, biochemical, physical or chemical functions of the molecule. It includes for example the enzymatic activity, the ability to interact with other molecules and ability to activate, facilitate, stabilize, inhibit, suppress or destabilize the function of other molecules, stability, ability to localize to certain subcellular locations. Where applicable, said term also relates to the function of a protein complex in its broadest sense.

The term "agonist" as used herein, means a molecule which modulates the formation of a protein complex or which, when bound to a complex or protein of the invention or a molecule in the protein complex, increases the amount of, or prolongs the duration of, the activity of the complex. The stimulation may be direct or indirect, including effects on the expression of a gene encoding a member of the protein complex, or by a competitive or non-competitive mechanism. Agonists may include proteins, nucleic acids, carbohydrates or any other organic or inorganic molecule or metals. Agonists also include a functional peptide or peptide fragment derived from a protein member of the complexes of the invention or a protein member itself of the complexes of the invention. Preferred activators are those which, when added to the complex and/or the protein of the invention under physiological conditions and/or in vitro assays, including diagnostic or prognostic assays, result in a change of the level of any of the activities of the protein complex and/or the proteins of the invention as exemplary illustrated above by at least 10%, at least 25%, at least 50%, at least 100%, at least, 200%, at least 500% or at least 1000% at a concentration of the activator  $1\mu\text{g ml}^{-1}$ ,  $10\mu\text{g ml}^{-1}$ ,  $100\mu\text{g ml}^{-1}$ ,  $500\mu\text{g ml}^{-1}$ ,  $1\text{mg ml}^{-1}$ ,  $10\text{mg ml}^{-1}$  or  $100\text{mg ml}^{-1}$ . Any combination of the

above mentioned degrees of percentages and concentration may be used to define an agonist of the invention, with greater effect at lower concentrations being preferred.

The term "amount" as used herein and as applicable to the embodiment described relates to the amount of the particular protein or protein complex described, including the value of null, i.e. where no protein or protein complex described in that particular embodiment is present under the or any of the conditions which might be specified in that particular embodiment.

The term "animal" as used herein includes, but is not limited to mammals, preferably mammals such as cows, pigs, horses, mice, rats, cats, dogs, sheep, goats and most preferably humans. Other animals used in agriculture, such as chickens, ducks etc. are also included in the definition as used herein.

The term "animal" as used herein does not include humans if being used in the context of genetic alterations to the germline.

The term "antagonist" as used herein, means a molecule which modulates the formation of a protein complex or which, when bound to a complex or protein of the invention or a molecule in the protein complex, decreases the amount of, or the duration or level of activity of the complex. The effect may be direct or indirect, including effects on the expression of a gene encoding a member of the protein complex, or by a competitive or non-competitive mechanism. Antagonists may include proteins, including antibodies, nucleic acids, carbohydrates or any other organic or anorganic molecule or metals. Antagonists also include a functional peptide or peptide fragment derived from a protein member of the complexes of the invention or a protein member itself of the complexes of the invention. Preferred antagonists are those which, when added to the complex and/or the protein of the invention under physiological conditions and/or in vitro assays, including diagnostic or prognostic assays, result in a change of the level of any of the activities of the protein complex and/or the proteins of the invention as exemplary illustrated above by at least 10%, at least 20%, at least 30%, at least 40% at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99% at a concentration of the inhibitor of  $1\mu\text{g ml}^{-1}$ ,  $10\mu\text{g ml}^{-1}$ ,  $100\mu\text{g ml}^{-1}$ ,  $500\mu\text{g ml}^{-1}$ ,  $1\text{mg ml}^{-1}$ ,  $10\text{mg ml}^{-1}$  or  $100\text{mg ml}^{-1}$ .

Any combination of the above mentioned degrees of percentages and concentration may be used to define antagonist of the invention, with greater effect at lower concentrations being preferred.

The term "antibodies" as used herein, include include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library.

The term "binding" as used herein means a stable or transient association between two molecules, including electrostatic, hydrophobic, ionic and/or hydrogen-bond interaction under physiological conditions and/or conditions being used in diagnostic or prognostic method or process or procedure.

The term "carrier" as used herein refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

If not stated otherwise, the terms "complex" and "protein complex" are used interchangeably herein and refer to a complex of proteins that is able to perform one or more functions of the wild type protein complex. The protein complex may or may not include and/or be associated with other molecules such as nucleic acid, such as RNA or

DNA, or lipids or further cofactors or moieties selected from a metal ions, hormones, second messengers, phosphate, sugars.

A "complex" of the invention may also be part of or a unit of a larger physiological protein assembly.

The term "component of the APP processing pathway" as used herein refers to a protein and/or protein complex which is involved in mediating APP processing in a cell. Components of the APP processing pathway include the following protein complexes as provided herein and components thereof:

APP-C59-complex, Bace1-complex, Bace2-complex, BRI-complex, mDab1-complex, Fe65L2-complex, Plit-complex, Paladin-complex, Neurotrypsin-complex, Hunc18a-complex, Telencephalin-complex, PC7-complex, TFCP2-complex, Jip1-complex, Lamezin-complex, VTRP-complex, p75-NTR-complex

If not stated otherwise, the term "compound" as used herein are include but are not limited to peptides, nucleic acids, carbohydrates, natural product extract librariesorganic molecules, preferentially small organic molecules, anorganic molecules, including but not limited to chemicals, metals and organometallic molecules.

The terms "derivatives" or "analogs of component proteins" or "variants" as used herein include, but are not limited, to molecules comprising regions that are substantially homologous to the component proteins, in various embodiments, by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to a sequence encoding the component protein under stringent, moderately stringent, or nonstringent conditions. It means a protein which is the outcome of a modification of the naturally occurring protein, by amino acid substitutions, deletions and additions, respectively, which derivatives still exhibit the biological function of the naturally occurring protein although not necessarily to the same degree. The biological function of such proteins can e.g. be examined by suitable available in vitro assays as provided in the invention.

The term "functionally active" as used herein refers to a polypeptide, namely a fragment or derivative, having structural, regulatory, or biochemical functions of the protein according to the embodiment of which this polypeptide, namely fragment or derivative is related to.



The term "fragment" as used herein refers to a polypeptide of at least 10, 20, 30, 40 or 50 amino acids of the component protein according to the embodiment. In specific embodiments, such fragments are not larger than 35, 100 or 200 amino acids.

The term "gene" as used herein refers to a nucleic acid comprising an open reading frame encoding a polypeptide of, if not stated otherwise, the present invention, including both exon and optionally intron sequences.

The terms "homologue" or "homologous gene products" as used herein mean a protein in another species, preferably mammals, which performs the same biological function as the a protein component of the complex further described herein. Such homologues are also termed "orthologous gene products". The algorithm for the detection of orthologue gene pairs from humans and mammals or other species uses the whole genome of these organisms. First, pairwise best hits are retrieved, using a full Smith-Waterman alignment of predicted proteins. To further improve reliability, these pairs are clustered with pairwise best hits involving *Drosophila melanogaster* and *C. elegans* proteins. Such analysis is given, e.g., in Nature, 2001, 409:860-921. The homologues of the proteins according to the invention can either be isolated based on the sequence homology of the genes encoding the proteins provided herein to the genes of other species by cloning the respective gene applying conventional technology and expressing the protein from such gene, or by isolating proteins of the other species by isolating the analogous complex according to the methods provided herein or to other suitable methods commonly known in the art.

The term "host cells" or, where applicable, "cells" or "hosts" as used herein is intended to be understood in a broadest sense and include, but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used. It is understood that this term not only refers to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The term "modification" as used herein refers to all modifications of a protein or protein complex of the invention including cleavage and addition or removal of a group.

The term "nucleic acid" as used herein refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). They may also be polynucleotides which include within them synthetic or modified nucleotides. A number of different types of modification to polynucleotides are known in the art. These include methylphosphonate and phosphorothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. For the purposes of the present invention, it is to be understood that the polynucleotides described herein may be modified by any method available in the art. Such modifications may be carried out in order to enhance the in vivo activity or lifespan of polynucleotides of the invention. Polynucleotides according to the invention may be produced recombinantly, synthetically, or by any means available to those of skill in the art. They may also be cloned by standard techniques. The polynucleotides are typically provided in isolated and/or purified form. As applicable to the embodiment being described, they include both single stranded and double-stranded polynucleotides.

The term "percent identity", as used herein, means the number of identical residues as defined by an optimal alignment using the Smith-Waterman algorithm divided by the length of the overlap multiplied by 100. The alignment is performed by the search program (Pearson, 1991, Genomics 11:635-650) with the constraint to align the maximum of both sequences.

The terms "polypeptides" and "proteins" are, where applicable, used interchangeably herein. They may be chemically modified, e.g. post-translationally modified. For example, they may be glycosylated or comprise modified amino acid residues. They may also be modified by the addition of a signal sequence to promote their secretion from a cell where the polypeptide does not naturally contain such a sequence. They may be tagged with a tag. They may be tagged with different labels which may assist in identification of the proteins in a protein complex. Polypeptides/proteins for use in the invention may be in a substantially isolated form. It will be understood that the polypeptide/protein may be mixed with carriers or diluents which will not interfere with the intended purpose of the polypeptide and still be regarded as substantially isolated. A polypeptide/protein for use in the invention may also be in a substantially purified form, in which case it will generally comprise the polypeptide in a

preparation in which more than 50%, e.g. more than 80%, 90%, 95% or 99%, by weight of the polypeptide in the preparation is a polypeptide of the invention.

"Target for therapeutic drug" means that the respective protein (target) can bind the active ingredient of a pharmaceutical composition and thereby changes its biological activity in response to the drug binding.

The term "tag" as used herein is meant to be understood in its broadest sense and to include, but is not limited to any suitable enzymatic, fluorescent, or radioactive labels and suitable epitopes, including but not limited to HA-tag, Myc-tag, T7, His-tag, FLAG-tag, Calmodulin binding proteins, glutathione-S-transferase, strep-tag, KT3-epitope, EEf-epitopes, green-fluorescent protein and variants thereof.

The term "therapeutics" as used herein, includes, but is not limited to, a protein complex of the present invention, the individual component proteins, and analogs and derivatives (including fragments); antibodies thereto; nucleic acids encoding the component protein, and analogs or derivatives thereof; component protein antisense nucleic acids, and agents that modulate complex formation and/or activity (i.e., agonists and antagonists).

The term "vector" as used herein means a nucleic acid molecule capable of transporting another nucleic acid sequence to which it has been linked. Preferred vectors are those capable of autonomous replication and/or expression of nucleic acids to which they linked. The terms "plasmid" and "vector" are used interchangeably herein when applicable to the embodiment. However, vectors other than plasmids are also included herein. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

#### 4. DETAILED DESCRIPTION OF THE INVENTION

##### Overview:

An object of the present invention was to identify protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the protein

complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said protein complex were identified. The components are listed in table 1.

Said object is further achieved by the characterisation of component proteins. These proteins are listed in table 2.

The invention thus relates to the following embodiments:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and a complex (II) comprising at least two of said second proteins,
 wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
2. A protein complex comprising a first protein selected from the proteins listed in table 1, fourth column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first

protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

3. A protein complex comprising all proteins selected from the proteins in table 1, third column of a given complex or at least one protein being a homologue thereof, or a variant thereof or functionally active fragment or functionally active derivative of said protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions; wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or at least one protein being a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, except at least one protein of the proteins listed in table 5, third column, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon

sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, with the proviso that the complex comprises at least one protein selected from table 1, fifth column of a given complex.

5. The complex of any of No. 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in at least one biochemical activity as stated in table 3.
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the protein, preferably the tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of a protein complex obtainable by a process according to any of No. 9 - 11.
13. Protein selected from the group of proteins in table 1, sixth column of a given complex or a homologue or a variant of thereof, or a functionally active fragment or a functionally active derivative of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
14. Nucleic acid encoding a protein according to No. 13.
15. Construct, preferably a vector construct, comprising
  - (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
  - (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, being selected from the second group of proteins according to No. 1 (b) or
  - (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to No. 1.

16. Host cell, containing a vector comprising at least one nucleic acid of No. 14 and /or a construct of No. 15 or containing several vectors each comprising at least one nucleic acid encoding at least one protein selected from the first group of proteins according to No. 1 (a) and at least one nucleic acid encoding at least one protein selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody containing the binding domain thereof which binds to any of the proteins of the group of proteins according to No. 13.
18. A kit comprising in one or more containers:
- (a) the complex of any of No. 1 - 8 and/or the proteins of No. 13 and/or
  - (b) an antibody according to No. 17 and/or
  - (c) a nucleic acid encoding a protein of the complex of any of No. 1 - 8 and/or a protein of No. 13 and/or
  - (d) cells expressing the complex of any of No. 1 - 8 and/or a protein of No. 13 and, optionally,
  - (e) further components such as reagents, buffers and working instructions.
19. The kit according to No. 18 for processing a substrate of a complex of any one of No. 1 - 8.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as those as stated in column 2, table 4 of a given complex.
21. Array, preferably a microarray, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 13 and/or at least one antibody according to No. 17 is attached to a solid carrier.



22. A process for modifying a substrate of a complex of any one of No. 1 - 8 comprising the step of bringing into contact a complex of any of No. 1 - 8 with said substrate, such that said substrate is modified.
23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or a protein according to No. 13.
24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders, preferentially for diseases or disorders such as those as stated in column 2, table 4 of a given complex.
25. A method for screening for a molecule that binds to a complex of any one of No. 1 - 8 and/or a protein of No. 13, comprising the following steps:
- (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.
26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of No. 1 - 8 comprising the steps of:
- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules

indicates that the molecule modulates function, activity, or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.
28. The method of No. 26, wherein the activity of said complex is determined.
29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
30. The method of No. 26, wherein the amount of the individual protein components of said complex is determined.
31. The method of No. 30, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as those as stated in column 2, table 4 of a given complex.
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as those as stated in column 2, table 4 of a given complex.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of No. 26 - 31 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.
36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.
40. The method of No. 39, wherein said determining step comprises determining whether any of the proteins according to No. 13 is present in the complex.

41. The complex of any one of No. 1 - 8, or a protein of No. 13 or an antibody or fragment thereof of No. 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as those as stated in column 2, table 4 of a given complex.
42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity of, or protein composition of, said complex.
43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of No. 1 - 8 and/or a protein as listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target, in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as a neurodegenerative disease such as those as stated in column 2, table 4 of a given complex.

Animal models are also provided herein.

Preferably, the protein components of the complexes described herein are all mammalian proteins. The complexes can also consist only of the respective homologues from other mammals such as mouse, rat, pig, cow, dog, monkey, sheep or horse or other species such as *D. melanogaster*, *C. elegans* or chicken. In another preferred embodiment, the complexes are a mixture of proteins from two or more species.

#### TABLES:

#### Table 1: Composition of Complexes

First column ('Name of complex'): Lists the name of the protein complexes as used herein.

Second column ('Entry point'): Lists the bait proteins that have been chosen for the purification of the given complex.

Third column ('All interactors'): Lists all novel interactors which have been identified as members of the complex and all interactors which have been known to be associated with the bait so far.

Fourth column ('Known interactors'): Lists all interactors which have been known to be associated with the bait so far.

Fifth column ('Novel interactors of the complex'): Lists all novel interactors of the complex which have been identified in the experiments provided herein.

Sixth column: Separately lists the members of the newly identified complex which have not been annotated previously.

#### Table 2: Individual Proteins of the Complexes

First column ('Protein'): Lists in alphabetical order all proteins which have been identified as interactors of the complexes presented herein.

Second column ('SEQ ID'): Lists the SEQ ID (Sequence Identifications) of the proteins herein as used herein.

Third column ('IPI-Numbers'): Lists the IPI-Numbers of the proteins herein. The IPI-Numbers refer to the International Protein Index created by the European Bioinformatics Institute (EMBL-EBI), Hinxton, UK.

Fourth column ('Molecular Weight'): Lists the Molecular Weight of the proteins in Dalton.

#### Table 3: Biochemical Activities of the Complexes of the invention.

First column ('Name of complex'): Lists the name of the protein complexes as used herein.

Second column ('Biochemical Activity'): Lists biochemical activities of the complexes. Assays in order to test these activities are also provided herein (infra).

#### Table 4: Medical Applications of the Complexes of the invention

First column ('Name of complex'): Lists the name of the protein complexes as used herein

Second column ('Medical application'): lists disorder, diseases, disease areas etc. which are treatable and/or preventable and/or diagnosable etc. by therapeutics and methods interacting with/acting via the complex.

#### 4.1 PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The protein complexes of the present invention and their component proteins are described in the Tables 1 - 4. The protein complexes and component proteins can be obtained by methods well known in the art for protein purification and recombinant protein expression. For example, the protein complexes of the present invention can be isolated using the TAP method described in Section 5, *infra*, and in WO 00/09716 and Rigaut et al., 1999, *Nature Biotechnol.* 17:1030-1032, which are each incorporated by reference in their entirety. Additionally, the protein complexes can be isolated by immunoprecipitation of the component proteins and combining the immunoprecipitated proteins. The protein complexes can also be produced by recombinantly expressing the component proteins and combining the expressed proteins.

The nucleic and amino acid sequences of the component proteins of the protein complexes of the present invention are provided herein (SEQ ID NO 1 - 249), and can be obtained by any method known in the art, e.g., by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of each sequence, and/or by cloning from a cDNA or genomic library using an oligonucleotide specific for each nucleotide sequence.

Homologues (e.g., nucleic acids encoding component proteins from other species) or other related sequences (e.g., variants, paralogs) which are members of a native cellular protein complex can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular nucleic acid sequence as a probe, using methods well known in the art for nucleic acid hybridization and cloning.

Exemplary moderately stringent hybridization conditions are as follows: prehybridization of filters containing DNA is carried out for 8 hours to overnight at 65°C in buffer composed of 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 µg/ml denatured salmon sperm DNA. Filters are hybridized for 48 hours at 65°C in prehybridization mixture containing 100 µg/ml denatured salmon sperm DNA and 5-20 X 10<sup>6</sup> cpm of <sup>32</sup>P-labeled probe. Washing of filters is done at 37°C

for 1 hour in a solution containing 2X SSC, 0.01% PVP, 0.01% Ficoll, and 0.01% BSA. This is followed by a wash in 0.1X SSC at 50 °C for 45 min before autoradiography. Alternatively, exemplary conditions of high stringency are as follows: e.g., hybridization to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel et al., eds., 1989, Current Protocols in Molecular Biology, Vol. 1, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3). Other conditions of high stringency which may be used are well known in the art. Exemplary low stringency hybridization conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 µg/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

For recombinant expression of one or more of the proteins, the nucleic acid containing all or a portion of the nucleotide sequence encoding the protein can be inserted into an appropriate expression vector, i.e., a vector that contains the necessary elements for the transcription and translation of the inserted protein coding sequence. The necessary transcriptional and translational signals can also be supplied by the native promoter of the component protein gene, and/or flanking regions.

A variety of host-vector systems may be utilized to express the protein coding sequence. These include but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

In a preferred embodiment, a complex of the present invention is obtained by expressing the entire coding sequences of the component proteins in the same cell, either under the control of the same promoter or separate promoters. In yet another embodiment, a derivative, fragment or homologue of a component protein is recombinantly expressed. Preferably the derivative, fragment or homologue of the protein forms a complex with the other components of the complex, and more preferably

forms a complex that binds to an anti-complex antibody. Such an antibody is further described infra.

Any method available in the art can be used for the insertion of DNA fragments into a vector to construct expression vectors containing a chimeric gene consisting of appropriate transcriptional/translational control signals and protein coding sequences. These methods may include in vitro recombinant DNA and synthetic techniques and in vivo recombinant techniques (genetic recombination). Expression of nucleic acid sequences encoding a component protein, or a derivative, fragment or homologue thereof, may be regulated by a second nucleic acid sequence so that the gene or fragment thereof is expressed in a host transformed with the recombinant DNA molecule(s). For example, expression of the proteins may be controlled by any promoter/enhancer known in the art. In a specific embodiment, the promoter is not native to the gene for the component protein. Promoters that may be used can be selected from among the many known in the art, and are chosen so as to be operative in the selected host cell.

In a specific embodiment, a vector is used that comprises a promoter operably linked to nucleic acid sequences encoding a component protein, or a fragment, derivative or homologue thereof, one or more origins of replication, and optionally, one or more selectable markers (e.g., an antibiotic resistance gene).

In another specific embodiment, an expression vector containing the coding sequence, or a portion thereof, of a component protein, either together or separately, is made by subcloning the gene sequences into the EcoRI restriction site of each of the three pGEX vectors (glutathione S-transferase expression vectors; Smith and Johnson, 1988, Gene 7:31-40). This allows for the expression of products in the correct reading frame.

Expression vectors containing the sequences of interest can be identified by three general approaches: (a) nucleic acid hybridization, (b) presence or absence of "marker" gene function, and (c) expression of the inserted sequences. In the first approach, coding sequences can be detected by nucleic acid hybridization to probes comprising sequences homologous and complementary to the inserted sequences. In the second approach, the recombinant vector/host system can be identified and selected based upon the presence or absence of certain "marker" functions (e.g., resistance to antibiotics, occlusion body formation in baculovirus, etc.) caused by insertion of the sequences of interest in the vector. For example, if a component protein gene, or portion



thereof, is inserted within the marker gene sequence of the vector, recombinants containing the encoded protein or portion will be identified by the absence of the marker gene function (e.g., loss of  $\beta$ -galactosidase activity). In the third approach, recombinant expression vectors can be identified by assaying for the component protein expressed by the recombinant vector. Such assays can be based, for example, on the physical or functional properties of the interacting species in in vitro assay systems, e.g., formation of a complex comprising the protein or binding to an anti-complex antibody.

Once recombinant component protein molecules are identified and the complexes or individual proteins isolated, several methods known in the art can be used to propagate them. Using a suitable host system and growth conditions, recombinant expression vectors can be propagated and amplified in quantity. As previously described, the expression vectors or derivatives which can be used include, but are not limited to, human or animal viruses such as vaccinia virus or adenovirus; insect viruses such as baculovirus, yeast vectors; bacteriophage vectors such as lambda phage; and plasmid and cosmid vectors.

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies or processes the expressed proteins in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically-engineered component proteins may be controlled. Furthermore, different host cells have characteristic and specific mechanisms for the translational and post-translational processing and modification (e.g., glycosylation, phosphorylation, etc.) of proteins. Appropriate cell lines or host systems can be chosen to ensure that the desired modification and processing of the foreign protein is achieved. For example, expression in a bacterial system can be used to produce an unglycosylated core protein, while expression in mammalian cells ensures "native" glycosylation of a heterologous protein. Furthermore, different vector/host expression systems may effect processing reactions to different extents.

In other specific embodiments, a component protein or a fragment, homologue or derivative thereof, may be expressed as fusion or chimeric protein product comprising the protein, fragment, homologue, or derivative joined via a peptide bond to a heterologous protein sequence of a different protein. Such chimeric products can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acids to each other by methods known in the art, in the proper coding frame, and expressing the chimeric products in a suitable host by methods commonly known in the

art. Alternatively, such a chimeric product can be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Chimeric genes comprising a portion of a component protein fused to any heterologous protein-encoding sequences may be constructed.

In particular, protein component derivatives can be made by altering their sequences by substitutions, additions or deletions that provide for functionally equivalent molecules. Due to the degeneracy of nucleotide coding sequences, other DNA sequences that encode substantially the same amino acid sequence as a component gene or cDNA can be used in the practice of the present invention. These include but are not limited to nucleotide sequences comprising all or portions of the component protein gene that are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. Likewise, the derivatives of the invention include, but are not limited to, those containing, as a primary amino acid sequence, all or part of the amino acid sequence of a component protein, including altered sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity that acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

In a specific embodiment, up to 1%, 2%, 5%, 10%, 15% or 20% of the total number of amino acids in the wild type protein are substituted or deleted; or 1, 2, 3, 4, 5, or 6 or up to 10 or up to 20 amino acids are inserted, substituted or deleted relative to the wild type protein.

In a specific embodiment of the invention, the nucleic acids encoding a protein component and protein components consisting of or comprising a fragment of or consisting of at least 6 (continuous) amino acids of the protein are provided. In other embodiments, the fragment consists of at least 10, 20, 30, 40, or 50 amino acids of the

component protein. In specific embodiments, such fragments are not larger than 35, 100 or 200 amino acids. Derivatives or analogs of component proteins include, but are not limited, to molecules comprising regions that are substantially homologous to the component proteins, in various embodiments, by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to a sequence encoding the component protein under stringent, moderately stringent, or nonstringent conditions.

In a specific embodiment, proteins are provided herein, which share an identical region of 20, 30, 40, 50 or 60 contiguous amino acids of the proteins listed in table 2.

The protein component derivatives and analogs of the invention can be produced by various methods known in the art. The manipulations which result in their production can occur at the gene or protein level. For example, the cloned gene sequences can be modified by any of numerous strategies known in the art (Sambrook et al., 1989, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York). The sequences can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated in vitro. In the production of the gene encoding a derivative, homologue or analog of a component protein, care should be taken to ensure that the modified gene retains the original translational reading frame, uninterrupted by translational stop signals, in the gene region where the desired activity is encoded.

Additionally, the encoding nucleic acid sequence can be mutated in vitro or in vivo, to create and/or destroy translation, initiation, and/or termination sequences, or to create variations in coding regions and/or form new restriction endonuclease sites or destroy pre-existing ones, to facilitate further in vitro modification. Any technique for mutagenesis known in the art can be used, including but not limited to, chemical mutagenesis and in vitro site-directed mutagenesis (Hutchinson et al., 1978, *J. Biol. Chem.* 253:6551-6558), amplification with PCR primers containing a mutation, etc.

Once a recombinant cell expressing a component protein, or fragment or derivative thereof, is identified, the individual gene product or complex can be isolated and analyzed. This is achieved by assays based on the physical and/or functional properties of the protein or complex, including, but not limited to, radioactive labeling of

the product followed by analysis by gel electrophoresis, immunoassay, cross-linking to marker-labeled product, etc.

The component proteins and complexes may be isolated and purified by standard methods known in the art (either from natural sources or recombinant host cells expressing the complexes or proteins), including but not restricted to column chromatography (e.g., ion exchange, affinity, gel exclusion, reversed-phase high pressure, fast protein liquid, etc.), differential centrifugation, differential solubility, or by any other standard technique used for the purification of proteins. Functional properties may be evaluated using any suitable assay known in the art.

Alternatively, once a component protein or its derivative, is identified, the amino acid sequence of the protein can be deduced from the nucleic acid sequence of the chimeric gene from which it was encoded. As a result, the protein or its derivative can be synthesized by standard chemical methods known in the art (e.g., Hunkapiller et al., 1984, Nature 310:105-111).

Manipulations of component protein sequences may be made at the protein level. Included within the scope of the invention is a complex in which the component proteins or derivatives and analogs that are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ , acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, etc.

In specific embodiments, the amino acid sequences are modified to include a fluorescent label. In another specific embodiment, the protein sequences are modified to have a heterofunctional reagent; such heterofunctional reagents can be used to crosslink the members of the complex.

In addition, complexes of analogs and derivatives of component proteins can be chemically synthesized. For example, a peptide corresponding to a portion of a component protein, which comprises the desired domain or mediates the desired activity in vitro (e.g., complex formation) can be synthesized by use of a peptide synthesizer. Furthermore, if desired, non-classical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the protein sequence.

In cases where natural products are suspected of being mutant or are isolated from new species, the amino acid sequence of a component protein isolated from the natural source, as well as those expressed in vitro, or from synthesized expression vectors in vivo or in vitro, can be determined from analysis of the DNA sequence, or alternatively, by direct sequencing of the isolated protein. Such analysis can be performed by manual sequencing or through use of an automated amino acid sequenator.

The complexes can also be analyzed by hydrophilicity analysis (Hopp and Woods, 1981, Proc. Natl. Acad. Sci. USA 78:3824-3828). A hydrophilicity profile can be used to identify the hydrophobic and hydrophilic regions of the proteins, and help predict their orientation in designing substrates for experimental manipulation, such as in binding experiments, antibody synthesis, etc. Secondary structural analysis can also be done to identify regions of the component proteins, or their derivatives, that assume specific structures (Chou and Fasman, 1974, Biochemistry 13:222-23). Manipulation, translation, secondary structure prediction, hydrophilicity and hydrophobicity profile predictions, open reading frame prediction and plotting, and determination of sequence homologies, etc., can be accomplished using computer software programs available in the art.

Other methods of structural analysis including but not limited to X-ray crystallography (Engstrom, 1974, Biochem. Exp. Biol. 11:7-13), mass spectroscopy and gas chromatography (Methods in Protein Science, J. Wiley and Sons, New York, 1997), and computer modeling (Fletterick and Zoller, eds., 1986, Computer Graphics and Molecular Modeling, In: Current Communications in Molecular Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, New York) can also be employed.

#### 4.2 ANTIBODIES TO PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

According to the present invention, a protein complex of the present invention comprising a first protein, or a functionally active fragment or functionally active derivative thereof, selected from the group consisting of proteins listed in fourth column of table 1; and a second protein, or a functionally active fragment or functionally active derivative thereof, selected from the group consisting of proteins listed in fifth column of table 1, or a functionally active fragment or functionally active derivative thereof, can be used as an immunogen to generate antibodies which immunospecifically bind such

immunogen. According to the present invention, also a protein complex of the present invention can be used as an immunogen to generate antibodies which immunospecifically bind to such immunogen comprising all proteins listed in fifth column of table 1.

Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library. In a specific embodiment, antibodies to a complex comprising human protein components are produced. In another embodiment, a complex formed from a fragment of said first protein and a fragment of said second protein, which fragments contain the protein domain that interacts with the other member of the complex, are used as an immunogen for antibody production. In a preferred embodiment, the antibody specific for the complex in that the antibody does not bind the individual protein components of the complex.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a polypeptide of the invention as an immunogen. Preferred polyclonal antibody compositions are ones that have been selected for antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred polyclonal antibody preparations are ones that contain only antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a polypeptide of the invention. In such a manner, the only human epitope or epitopes recognized by the resulting antibody compositions raised against this immunogen will be present as part of a polypeptide or polypeptides of the invention.

The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. Alternatively, antibodies specific for a protein or polypeptide of the invention can be selected for (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies

specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, i.e., one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those on the desired protein or polypeptide of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein or polypeptide of the invention.

At an appropriate time after immunization, e.g., when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, 1975, *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al., 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al., 1985, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* 1994, Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al.,

1991, *Bio/Technology* 9:1370-1372; Hay et al., 1992, *Hum. Antibod. Hybridomas* 3:81-85; Huse et al., 1989, *Science* 246:1275-1281; Griffiths et al., 1993, *EMBO J.* 12:725-734.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, e.g., Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, e.g., Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al., 1988, *Science* 240:1041-1043; Liu et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al., 1987, *J. Immunol.* 139:3521-3526; Sun et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al., 1987, *Canc. Res.* 47:999-1005; Wood et al., 1985, *Nature* 314:446-449; and Shaw et al., 1988, *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, 1985, *Science* 229:1202-1207; Oi et al., 1986, *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones et al., 1986, *Nature* 321:552-525; Verhoeyan et al., 1988, *Science* 239:1534; and Beidler et al., 1988, *J. Immunol.* 141:4053-4060.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell



differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, 1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., 1994, *Bio/technology* 12:899-903).

Antibody fragments that contain the idiotypes of the complex can be generated by techniques known in the art. For example, such fragments include, but are not limited to, the F(ab')<sub>2</sub> fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragment that can be generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragment; the Fab fragment that can be generated by treating the antibody molecular with papain and a reducing agent; and Fv fragments.

In the production of antibodies, screening for the desired antibody can be accomplished by techniques known in the art, e.g., ELISA (enzyme-linked immunosorbent assay). To select antibodies specific to a particular domain of the complex, or a derivative thereof, one may assay generated hybridomas for a product that binds to the fragment of the complex, or a derivative thereof, that contains such a domain. For selection of an antibody that specifically binds a complex of the present, or a derivative, or homologue thereof, but which does not specifically bind to the individual proteins of the complex, or a derivative, or homologue thereof, one can select on the basis of positive binding to the complex and a lack of binding to the individual protein components.

Antibodies specific to a domain of the complex, or a derivative, or homologue thereof, are also provided.

The foregoing antibodies can be used in methods known in the art relating to the localization and/or quantification of the complexes of the invention, e.g., for imaging these proteins, measuring levels thereof in appropriate physiological samples (by immunoassay), in diagnostic methods, etc. This hold true also for a derivative, or homologue thereof of a complex.

In another embodiment of the invention (see *infra*), an antibody to a complex or a fragment of such antibodies containing the antibody binding domain, is a therapeutic.

#### 4.3 DIAGNOSTIC, PROGNOSTIC, AND SCREENING USES OF THE PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The particular protein complexes and proteins of the present invention may be markers of normal physiological processes, and thus have diagnostic utility. Further, definition of particular groups of patients with elevations or deficiencies of a protein complex of the present invention, or wherein the protein complex has a change in protein component composition, can lead to new nosological classifications of diseases, furthering diagnostic ability.

Examples for diseases or disorders are those as listed in table 4

Detecting levels of protein complexes, or individual component proteins that form the complexes, or detecting levels of the mRNAs encoding the components of the complex, may be used in diagnosis, prognosis, and/or staging to follow the course of a disease state, to follow a therapeutic response, etc.

A protein complex of the present invention and the individual components of the complex and a derivative, analog or subsequence thereof, encoding nucleic acids (and sequences complementary thereto), and anti-complex antibodies and antibodies directed against individual components that can form the complex, are useful in diagnostics. The foregoing molecules can be used in assays, such as immunoassays, to detect, prognose, diagnose, or monitor various conditions, diseases, and disorders characterized by aberrant levels of a complex or aberrant component composition of a complex, or monitor the treatment of such various conditions, diseases, and disorders.

In particular, such an immunoassay is carried out by a method comprising contacting a sample derived from a patient with an anti-complex antibody under conditions such that immunospecific binding can occur, and detecting or measuring the

amount of any immunospecific binding by the antibody. In a specific aspect, such binding of antibody, in tissue sections, can be used to detect aberrant complex localization, or aberrant (e.g., high, low or absent) levels of a protein complex or complexes. In a specific embodiment, an antibody to the complex can be used to assay a patient tissue or serum sample for the presence of the complex, where an aberrant level of the complex is an indication of a diseased condition. By "aberrant levels" is meant increased or decreased levels relative to that present, or a standard level representing that present, in an analogous sample from a portion or fluid of the body, or from a subject not having the disorder.

The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as Western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few known in the art.

Nucleic acids encoding the components of the protein complex and related nucleic acid sequences and subsequences, including complementary sequences, can be used in hybridization assays. The nucleic acid sequences, or subsequences thereof, comprising about at least 8 nucleotides, can be used as hybridization probes. Hybridization assays can be used to detect, prognose, diagnose, or monitor conditions, disorders, or disease states associated with aberrant levels of the mRNAs encoding the components of a complex as described, supra. In particular, such a hybridization assay is carried out by a method comprising contacting a sample containing nucleic acid with a nucleic acid probe capable of hybridizing to component protein coding DNA or RNA, under conditions such that hybridization can occur, and detecting or measuring any resulting hybridization.

In specific embodiments, diseases and disorders involving or characterized by aberrant levels of a protein complex or aberrant complex composition can be diagnosed, or its suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by determining the component protein composition of the complex, or detecting aberrant levels of a member of the complex or un-complexed component proteins or encoding nucleic acids, or functional activity including, but not restricted to, binding to an interacting partner, or by detecting mutations in component

protein RNA, DNA or protein (e.g., mutations such as translocations, truncations, changes in nucleotide or amino acid sequence relative to wild-type that cause increased or decreased expression or activity of a complex, and/or component protein.

Such diseases and disorders include, but are not limited to neurodegenerative disease such as listed in table 4.

By way of example, levels of a protein complex and the individual components of a complex can be detected by immunoassay, levels of component protein RNA or DNA can be detected by hybridization assays (e.g., Northern blots, dot blots, RNase protection assays), and binding of component proteins to each other (e.g., complex formation) can be measured by binding assays commonly known in the art. Translocations and point mutations in component protein genes can be detected by Southern blotting, RFLP analysis, PCR using primers that preferably generate a fragment spanning at least most of the gene by sequencing of genomic DNA or cDNA obtained from the patient, etc.

Assays well known in the art (e.g., assays described above such as immunoassays, nucleic acid hybridization assays, activity assays, etc.) can be used to determine whether one or more particular protein complexes are present at either increased or decreased levels, or are absent, in samples from patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, as compared to the levels in samples from subjects not having such a disease or disorder, or having a predisposition to develop such a disease or disorder. Additionally, these assays can be used to determine whether the ratio of the complex to the un-complexed components of the complex, is increased or decreased in samples from patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, as compared to the ratio in samples from subjects not having such a disease or disorder.

In the event that levels of one or more particular protein complexes (i.e., complexes formed from component protein derivatives, homologs, fragments, or analogs) are determined to be increased in patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, then the particular disease or disorder, or predisposition for a disease or disorder, can be diagnosed, have prognosis defined for, be screened for, or be monitored by detecting increased levels of the one or more protein complexes, increased levels of the mRNA

that encodes one or more members of the one or more particular protein complexes, or by detecting increased complex functional activity.

Accordingly, in a specific embodiment of the present invention, diseases and disorders involving increased levels of one or more protein complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting increased levels of the one or more protein complexes, the mRNA encoding both members of the complex, or complex functional activity, or by detecting mutations in the component proteins that stabilize or enhance complex formation, e.g., mutations such as translocations in nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type, that stabilize or enhance complex formation.

In the event that levels of one or more particular protein complexes are determined to be decreased in patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, then the particular disease or disorder or predisposition for a disease or disorder can be diagnosed, have its prognosis determined, be screened for, or be monitored by detecting decreased levels of the one or more protein complexes, the mRNA that encodes one or more members of the particular one or more protein complexes, or by detecting decreased protein complex functional activity.

Accordingly, in a specific embodiment of the invention, diseases and disorders involving decreased levels of one or more protein complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting decreased levels of the one or more protein complexes, the mRNA encoding one or more members of the one or more complexes, or complex functional activity, or by detecting mutations in the component proteins that decrease complex formation, e.g., mutations such as translocations in nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type, that decrease complex formation.

Accordingly, in a specific embodiment of the invention, diseases and disorders involving aberrant compositions of the complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting the component proteins of one or more complexes, or the mRNA encoding the members of the one or more complexes.

The use of detection techniques, especially those involving antibodies against a protein complex, provides a method of detecting specific cells that express the complex or component proteins. Using such assays, specific cell types can be defined in which one or more particular protein complexes are expressed, and the presence of the complex or component proteins can be correlated with cell viability, state, health, etc.

Also embodied are methods to detect a protein complex of the present invention in cell culture models that express particular protein complexes or derivatives thereof, for the purpose of characterizing or preparing the complexes for harvest. This embodiment includes cell sorting of prokaryotes such as but not restricted to bacteria (Davey and Kell, 1996, *Microbiol. Rev.* 60:641-696), primary cultures and tissue specimens from eukaryotes, including mammalian species such as human (Steele et al., 1996, *Clin. Obstet. Gynecol* 39:801-813), and continuous cell cultures (Orfao and Ruiz-Arguelles, 1996, *Clin. Biochem.* 29:5-9). Such isolations can be used as methods of diagnosis, described, *supra*.

In a further specific embodiment, a modulation of the formation process of a complex can be determined.

Such a modulation can either be a change in the typical time course of its formation or a change in the typical steps leading to the formation of the complete complex.

Such changes can for example be detected by analysing and comparing the process of complex formation in untreated wild type cells of a particular type and/or cells showing or having the predisposition to develop a certain disease phenotype and/or cells which have been treated with particular conditions and/or particular agents in a particular situation.

Methods to study such changes in time course are well known in the art and include for example Western-blot analysis of the proteins in the complex isolated at different steps of its formation.

Furthermore an aberrant intracellular localization of the protein complex and/or an aberrant transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or a gene dependent on the complex can serve as a marker for a disease and thus have diagnostic utility for any disease which is caused by an aberrant activity, function, composition or formation of the complex of the invention.

Methods to study the intracellular localization are well known in the art and include, but are not limited to immunofluorescence analysis using antibodies specific for components of the protein. Preferentially, double-stainings including staining of other cellular structures are being used to facilitate the detection of the intracellular localization. Methods to analyse the transcription levels of a gene dependent on the complex are also well known in the art and include Northern blot analysis, quantitative PCR etc. The abundance of proteins dependent on the protein can be analyzed as described supra. Methods to study changes in the activity of proteins dependent on complex depend on the protein. The choice of such methods will be apparent to any person skilled in the art.

#### 4.4 THERAPEUTIC USES OF PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The present invention is directed to a method for treatment or prevention of various diseases and disorders by administration of a therapeutic compound (termed herein "therapeutic"). Such "therapeutics" include, but are not limited to, a protein complex of the present invention, the individual component proteins, and analogs and derivatives (including fragments) of the foregoing (e.g., as described hereinabove); antibodies thereto (as described hereinabove); nucleic acids encoding the component protein, and analogs or derivatives, thereof (e.g., as described hereinabove); component protein antisense nucleic acids, and agents that modulate complex formation and/or activity (i.e., agonists and antagonists).

The protein complexes as identified herein can be implicated in processes which are implicated in or associated with pathological conditions.

Diseases and disorders which can be treated and/or prevented and/or diagnosed by therapeutics interacting with any of the complexes provided herein are for example those listed in table 4.

These disorders are treated or prevented by administration of a therapeutic that modulates (i.e. inhibits or promotes) protein complex activity or formation or modulates its function or composition. Diseases or disorders associated with aberrant levels of complex activity or formation, or aberrant levels or activity of the component proteins, or aberrant complex composition or a change in the function, may be treated by

administration of a therapeutic that modulates complex formation or activity or by the administration of a protein complex.

Therapeutics may also be administered to modulate complex formation or activity or level thereof in a microbial organism such as yeast, fungi such as *Candida albicans* causing an infectious disease in animals or humans.

Diseases and disorders characterized by increased (relative to a subject not suffering from the disease or disorder) complex levels or activity can be treated with therapeutics that antagonize (i.e., reduce or inhibit) complex formation or activity. Therapeutics that can be used include, but are not limited to, the component proteins or an analog, derivative or fragment of the component protein; anti-complex antibodies (e.g., antibodies specific for the protein complex, or a fragment or derivative of the antibody containing the binding region thereof; nucleic acids encoding the component proteins; antisense nucleic acids complementary to nucleic acids encoding the component proteins; and nucleic acids encoding the component protein that are dysfunctional due to, e.g., a heterologous insertion within the protein coding sequence, that are used to "knockout" endogenous protein function by homologous recombination, see, e.g., Capecchi, 1989, *Science* 244:1288-1292. In one embodiment, a therapeutic is 1, 2 or more antisense nucleic acids which are complementary to 1, 2, or more nucleic acids, respectively, that encode component proteins of a complex.

In a specific embodiment of the present invention, a nucleic acid containing a portion of a component protein gene in which gene sequences flank (are both 5' and 3' to) a different gene sequence, is used as a component protein antagonist, or to promote component protein inactivation by homologous recombination (see also, Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342: 435-438). Additionally, mutants or derivatives of a component protein that has greater affinity for another component protein or the complex than wild type may be administered to compete with wild type protein for binding, thereby reducing the levels of complexes containing the wild type protein. Other therapeutics that inhibit complex function can be identified by use of known convenient *in vitro* assays, e.g., based on their ability to inhibit complex formation, or as described in Section 4.5, *infra*.

In specific embodiments, therapeutics that antagonize complex formation or activity are administered therapeutically, including prophylactically, (1) in diseases or disorders involving an increased (relative to normal or desired) level of a complex, for example, in patients where complexes are overactive or overexpressed; or (2) in



diseases or disorders where an in vitro (or in vivo) assay (see *infra*) indicates the utility of antagonist administration. Increased levels of a complex can be readily detected, e.g., by quantifying protein and/or RNA, by obtaining a patient tissue sample (e.g., from biopsy tissue) and assaying it in vitro for RNA or protein levels, or structure and/or activity of the expressed complex (or the encoding mRNA). Many methods standard in the art can be thus employed including, but not limited to, immunoassays to detect complexes and/or visualize complexes (e.g., Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE], immunocytochemistry, etc.), and/or hybridization assays to detect concurrent expression of component protein mRNA (e.g., Northern assays, dot blot analysis, in situ hybridization, etc.).

A more specific embodiment of the present invention is directed to a method of reducing complex expression (i.e., expression of the protein components of the complex and/or formation of the complex) by targeting mRNAs that express the protein moieties. RNA therapeutics currently fall within three classes, antisense species, ribozymes, or RNA aptamers (Good et al., 1997, *Gene Therapy* 4:45-54).

Antisense oligonucleotides have been the most widely used. By way of example, but not limitation, antisense oligonucleotide methodology to reduce complex formation is presented below, *infra*. Ribozyme therapy involves the administration, induced expression, etc. of small RNA molecules with enzymatic ability to cleave, bind, or otherwise inactivate specific RNAs, to reduce or eliminate expression of particular proteins (Grassi and Marini, 1996, *Annals of Medicine* 28:499-510; Gibson, 1996, *Cancer and Metastasis Reviews* 15:287-299). RNA aptamers are specific RNA ligand proteins, such as for Tat and Rev RNA (Good et al., 1997, *Gene Therapy* 4:45-54) that can specifically inhibit their translation. Aptamers specific for component proteins can be identified by many methods well known in the art, for example, by affecting the formation of a complex in the protein-protein interaction assay described, *infra*.

In another embodiment, the activity or levels of a component protein are reduced by administration of another component protein, or the encoding nucleic acid, or an antibody that immunospecifically binds to the component protein, or a fragment or a derivative of the antibody containing the binding domain thereof.

In another aspect of the invention, diseases or disorders associated with increased levels of an component protein of the complex may be treated or prevented by administration of a therapeutic that increases complex formation if the complex formation

acts to reduce or inactivate the component protein through complex formation. Such diseases or disorders can be treated or prevented by administration of one component member of the complex, administration of antibodies or other molecules that stabilize the complex, etc.

Diseases and disorders associated with underexpression of a complex, or a component protein, are treated or prevented by administration of a therapeutic that promotes (i.e., increases or supplies) complex levels and/or function, or individual component protein function. Examples of such a therapeutic include but are not limited to a complex or a derivative, analog or fragment of the complex that are functionally active (e.g., able to form a complex), un-complexed component proteins and derivatives, analogs, and fragments of un-complexed component proteins, and nucleic acids encoding the members of a complex or functionally active derivatives or fragments of the members of the complex, e.g., for use in gene therapy. In a specific embodiment, a therapeutic includes derivatives, homologs or fragments of a component protein that increase and/or stabilize complex formation. Examples of other agonists can be identified using in vitro assays or animal models, examples of which are described, *infra*.

In yet other specific embodiments of the present invention, therapeutics that promote complex function are administered therapeutically, including prophylactically, (1) in diseases or disorders involving an absence or decreased (relative to normal or desired) level of a complex, for example, in patients where a complex, or the individual components necessary to form the complex, is lacking, genetically defective, biologically inactive or underactive, or under-expressed; or (2) in diseases or disorders wherein an in vitro or in vivo assay (see, *infra*) indicates the utility of complex agonist administration. The absence or decreased level of a complex, component protein or function can be readily detected, e.g., by obtaining a patient tissue sample (e.g., from biopsy tissue) and assaying it in vitro for RNA or protein levels, structure and/or activity of the expressed complex and/or the concurrent expression of mRNA encoding the two components of the complex. Many methods standard in the art can be thus employed, including but not limited to immunoassays to detect and/or visualize a complex, or the individual components of a complex (e.g., Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE], immunocytochemistry, etc.) and/or hybridization assays to detect expression of mRNAs encoding the individual protein components of a complex by detecting and/or visualizing

component mRNA concurrently or separately using, e.g., Northern assays, dot blot analysis, in situ hybridization, etc.

In specific embodiments, the activity or levels of a component protein are increased by administration of another component protein of the same complex, or a derivative, homolog or analog thereof, a nucleic acid encoding the other component, or an agent that stabilizes or enhances the other component, or a fragment or derivative of such an agent.

Generally, administration of products of species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, a human complex, or derivative, homolog or analog thereof; nucleic acids encoding the members of the human complex or a derivative, homolog or analog thereof; an antibody to a human complex, or a derivative thereof; or other human agents that affect component proteins or the complex, are therapeutically or prophylactically administered to a human patient.

Preferably, suitable in vitro or in vivo assays are utilized to determine the effect of a specific therapeutic and whether its administration is indicated for treatment of the affected tissue or individual.

In various specific embodiments, in vitro assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if a therapeutic has a desired effect upon such cell types.

Compounds for use in therapy can be tested in suitable animal model systems prior to testing in humans, including, but not limited to, rats, mice, chicken, cows, monkeys, rabbits, etc. For in vivo testing, prior to administration to humans, any animal model system known in the art may be used. Additional descriptions and sources of therapeutics that can be used according to the invention are found in Sections 4.1 to 4.3 and 4.7 herein.

#### 4.4.1 GENE THERAPY

In a specific embodiment of the present invention, nucleic acids comprising a sequence encoding the component proteins, or a functional derivative thereof, are administered to modulate complex activity or formation by way of gene therapy. Gene therapy refers to therapy performed by the administration of a nucleic acid to a subject.

In this embodiment of the present invention, the nucleic acid expresses its encoded protein(s) that mediates a therapeutic effect by modulating complex activity or formation. Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., 1993, *Clinical Pharmacy* 12:488-505; Wu and Wu, 1991, *Biotherapy* 3:87-95; Tolstoshev, 1993, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596; Mulligan, 1993, *Science* 260:926-932; Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62:191-217; and May, 1993, *TIBTECH* 11:155-215. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al., eds., 1993, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY; and Kriegler, 1990, *Gene Transfer and Expression*, A Laboratory Manual, Stockton Press, NY.

In a preferred aspect, the therapeutic comprises a nucleic acid that is part of an expression vector that expresses one or more of the component proteins, or fragments or chimeric proteins thereof, in a suitable host. In particular, such a nucleic acid has a promoter operably linked to the protein coding region(s) (or, less preferably separate promoters linked to the separate coding regions separately), said promoter being inducible or constitutive, and optionally, tissue-specific. In another particular embodiment, a nucleic acid molecule is used in which the coding sequences, and any other desired sequences, are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intra-chromosomal expression of the component protein nucleic acids (Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342:435-438).

Delivery of the nucleic acid into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vector, or indirect, in which case, cells are first transformed with the nucleic acid in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid is directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by infection using a defective or attenuated retroviral or other viral vector (U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle

bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors, or through use of transfecting agents, by encapsulation in liposomes, microparticles, or microcapsules, or by administering it in linkage to a peptide that is known to enter the nucleus, or by administering it in linkage to a ligand subject to receptor-mediated endocytosis that can be used to target cell types specifically expressing the receptors (e.g., Wu and Wu, 1987, *J. Biol. Chem.* 262:4429-4432), etc. In another embodiment, a nucleic acid-ligand complex can be formed in which the ligand comprises a fusogenic viral peptide that disrupts endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., International Patent Publications WO 92/06180; WO 92/22635; WO 92/20316; WO 93/14188; and WO 93/20221. Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342:435-438).

In a specific embodiment, a viral vector that contains the component protein encoding nucleic acids is used. For example, a retroviral vector can be used (Miller et al., 1993, *Meth. Enzymol.* 217:581-599). These retroviral vectors have been modified to delete retroviral sequences that are not necessary for packaging of the viral genome and integration into host cell DNA. The encoding nucleic acids to be used in gene therapy is/are cloned into the vector, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., 1994, *Biotherapy* 6:291-302, which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are Clowes et al., 1994, *J. Clin. Invest.* 93:644-651; Kiem et al., 1994, *Blood* 83:1467-1473; Salmons and Gunzberg, 1993, *Human Gene Therapy* 4:129-141; and Grossman and Wilson, 1993, *Curr. Opin. in Genetics and Devel.* 3:110-114.

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are the liver, the central nervous system, endothelial cells and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, 1993, *Curr. Opin.*

Genet. Devel. 3:499-503, discuss adenovirus-based gene therapy. The use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys has been demonstrated by Bout et al., 1994, Human Gene Therapy 5:3-10. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., 1991, Science 252:431-434; Rosenfeld et al., 1992, Cell 68:143-155; and Mastrangeli et al., 1993, J. Clin. Invest. 91:225-234.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., 1993, Proc. Soc. Exp. Biol. Med. 204:289-300).

Another approach to gene therapy involves transferring a gene into cells in tissue culture by methods such as electroporation, lipofection, calcium phosphate-mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene from those that have not. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art including, but not limited to, transfection by electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, 1993, Meth. Enzymol. 217:599-618; Cohen et al., 1993, Meth. Enzymol. 217:618-644; Cline, 1985, Pharmac. Ther. 29:69-92) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably, is heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. In a preferred embodiment, epithelial cells are injected, e.g., subcutaneously. In another embodiment, recombinant skin cells may be applied as a skin graft onto the patient. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes, blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, and granulocytes, various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, a component protein encoding nucleic acid is/are introduced into the cells such that the gene or genes are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention. Such stem cells include but are not limited to hematopoietic stem cells (HSCs), stem cells of epithelial tissues such as the skin and the lining of the gut, embryonic heart muscle cells, liver stem cells (International Patent Publication WO 94/08598), and neural stem cells (Stemple and Anderson, 1992, Cell 71:973-985).

Epithelial stem cells (ESCs), or keratinocytes, can be obtained from tissues such as the skin and the lining of the gut by known procedures (Rheinwald, 1980, Meth. Cell Biol. 2A:229). In stratified epithelial tissue such as the skin, renewal occurs by mitosis of stem cells within the germinal layer, the layer closest to the basal lamina. Similarly, stem cells within the lining of the gut provide for a rapid renewal rate of this tissue. ESCs or keratinocytes obtained from the skin or lining of the gut of a patient or donor can be grown in tissue culture (Rheinwald, 1980, Meth. Cell Bio. 2A:229; Pittelkow and Scott, 1986, Mayo Clinic Proc. 61:771). If the ESCs are provided by a donor, a method for suppression of host versus graft reactivity (e.g., irradiation, or drug or antibody administration to promote moderate immunosuppression) can also be used.

With respect to hematopoietic stem cells (HSCs), any technique that provides for the isolation, propagation, and maintenance in vitro of HSCs can be used in this embodiment of the invention. Techniques by which this may be accomplished include (a) the isolation and establishment of HSC cultures from bone marrow cells isolated from the future host, or a donor, or (b) the use of previously established long-term HSC

cultures, which may be allogeneic or xenogeneic. Non-autologous HSCs are used preferably in conjunction with a method of suppressing transplantation immune reactions between the future host and patient. In a particular embodiment of the present invention, human bone marrow cells can be obtained from the posterior iliac crest by needle aspiration (see, e.g., Kodo et al., 1984, J. Clin. Invest. 73: 1377-1384). In a preferred embodiment of the present invention, the HSCs can be made highly enriched or in substantially pure form. This enrichment can be accomplished before, during, or after long-term culturing, and can be done by any technique known in the art. Long-term cultures of bone marrow cells can be established and maintained by using, for example, modified Dexter cell culture techniques (Dexter et al., 1977, J. Cell Physiol. 91:335) or Witlock-Witte culture techniques (Witlock and Witte, 1982, Proc. Natl. Acad. Sci. USA 79:3608-3612).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Additional methods can be adapted for use to deliver a nucleic acid encoding the component proteins, or functional derivatives thereof, e.g., as described in Section 4.1, supra.

#### 4.4.2 USE OF ANTISENSE OLIGONUCLEOTIDES FOR SUPPRESSION OF PROTEIN COMPLEX FORMATION OR PROTEIN COMPLEX/PROTEIN ACTIVITY

In a specific embodiment of the present invention, protein complex activity and formation and protein activity is inhibited by use of antisense nucleic acids for the component proteins of the complex, that inhibit transcription and/or translation of their complementary sequence. The present invention provides the therapeutic or prophylactic use of nucleic acids of at least six nucleotides that are antisense to a gene or cDNA encoding a component protein, or a portion thereof. An "antisense" nucleic acid as used herein refers to a nucleic acid capable of hybridizing to a sequence-specific portion of a component protein RNA (preferably mRNA) by virtue of some sequence complementarity. The antisense nucleic acid may be complementary to a coding and/or noncoding region of a component protein mRNA. Such antisense nucleic acids that



inhibit complex formation or activity have utility as therapeutics, and can be used in the treatment or prevention of disorders as described supra.

The antisense nucleic acids of the invention can be oligonucleotides that are double-stranded or single-stranded, RNA or DNA, or a modification or derivative thereof, which can be directly administered to a cell, or which can be produced intracellularly by transcription of exogenous, introduced sequences.

In another embodiment, the present invention is directed to a method for inhibiting the expression of component protein nucleic acid sequences, in a prokaryotic or eukaryotic cell, comprising providing the cell with an effective amount of a composition comprising an antisense nucleic acid of the component protein, or a derivative thereof, of the invention.

The antisense nucleic acids are of at least six nucleotides and are preferably oligonucleotides, ranging from 6 to about 200 nucleotides. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 15 nucleotides, at least 100 nucleotides, or at least 200 nucleotides. The oligonucleotides can be DNA or RNA or chimeric mixtures, or derivatives or modified versions thereof, and either single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. USA 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. USA 84:648-652; International Patent Publication No. WO 88/09810) or blood-brain barrier (see, e.g., International Patent Publication No. WO 89/10134), hybridization-triggered cleavage agents (see, e.g., Krol et al., 1988, BioTechniques 6:958-976), or intercalating agents (see, e.g., Zon, 1988, Pharm. Res. 5:539-549).

In a preferred aspect of the invention, an antisense oligonucleotide is provided, preferably as single-stranded DNA. The oligonucleotide may be modified at any position in its structure with constituents generally known in the art.

The antisense oligonucleotides may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thio-uridine, 5-carboxymethylaminomethyluracil, dihydrouracil,  $\beta$ -D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine,

2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil,  $\beta$ -D-mannosylqueosine, 5N-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

In another embodiment, the oligonucleotide comprises at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal, or an analog of the foregoing.

In yet another embodiment, the oligonucleotide is a 2'- $\alpha$ -anomeric oligonucleotide. An  $\alpha$ -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641).

The oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization-triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

Oligonucleotides of the invention may be synthesized by standard methods known in the art, e.g., by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligo-nucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. USA 85:7448-7451), etc.

In a specific embodiment, the antisense oligonucleotides comprise catalytic RNAs, or ribozymes (see, e.g., International Patent Publication No. WO 90/11364; Sarver et al., 1990, Science 247:1222-1225). In another embodiment, the oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res.

15:6131-6148), or a chimeric RNA-DNA analog (Inoue et al., 1987, FEBS Lett. 215:327-330).

In an alternative embodiment, the antisense nucleic acids of the invention are produced intracellularly by transcription from an exogenous sequence. For example, a vector can be introduced in vivo such that it is taken up by a cell, within which cell the vector or a portion thereof is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the component protein. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art to be capable of replication and expression in mammalian cells. Expression of the sequences encoding the antisense RNAs can be by any promoter known in the art to act in mammalian, preferably human, cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, 1981, Nature 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., 1980, Cell 22:787-797), the herpes thymidine kinase promoter (Wagner et al., 1981, Proc. Natl. Acad. Sci. USA 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster et al., 1982, Nature 296:39-42), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a component protein gene, preferably a human gene. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with a component protein RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

The component protein antisense nucleic acids can be used to treat (or prevent) disorders of a cell type that expresses, or preferably overexpresses, a protein complex.

Cell types that express or overexpress component protein RNA can be identified by various methods known in the art. Such methods include, but are not limited to, hybridization with component protein-specific nucleic acids (e.g., by Northern blot hybridization, dot blot hybridization, or in situ hybridization), or by observing the ability of RNA from the cell type to be translated in vitro into the component protein by immunohistochemistry, Western blot analysis, ELISA, etc. In a preferred aspect, primary tissue from a patient can be assayed for protein expression prior to treatment, e.g., by immunocytochemistry, in situ hybridization, or any number of methods to detect protein or mRNA expression.

Pharmaceutical compositions of the invention (see Section 4.7, *infra*), comprising an effective amount of a protein component antisense nucleic acid in a pharmaceutically acceptable carrier can be administered to a patient having a disease or disorder that is of a type that expresses or overexpresses a protein complex of the present invention.

The amount of antisense nucleic acid that will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. Where possible, it is desirable to determine the antisense cytotoxicity in vitro, and then in useful animal model systems, prior to testing and use in humans.

In a specific embodiment, pharmaceutical compositions comprising antisense nucleic acids are administered via liposomes, microparticles, or microcapsules. In various embodiments of the invention, it may be useful to use such compositions to achieve sustained release of the antisense nucleic acids. In a specific embodiment, it may be desirable to utilize liposomes targeted via antibodies to specific identifiable central nervous system cell types (Leonetti et al., 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2448-2451; Renneisen et al., 1990, J. Biol. Chem. 265:16337-16342).

#### 4.5 ASSAYS OF PROTEIN COMPLEXES/PROTEINS OF THE INVENTION AND DERIVATIVES AND ANALOGS THEREOF

The functional activity of a protein complex of the present invention, or a derivative, fragment or analog thereof or protein component thereof, can be assayed by various methods. Potential modulators (e.g., agonists and antagonists) of complex

activity or formation, e.g., anti-complex antibodies and antisense nucleic acids, can be assayed for the ability to modulate complex activity or formation.

In one embodiment of the present invention, where one is assaying for the ability to bind or compete with a wild-type complex for binding to an anti-complex antibody, various immunoassays known in the art can be used, including but not limited to competitive and non-competitive assay systems using techniques such as radioimmunoassay, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitin reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels), western blot analysis, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

The expression of the component protein genes (both endogenous and those expressed from cloned DNA containing the genes) can be detected using techniques known in the art, including but not limited to Southern hybridization (Southern, 1975, J. Mol. Biol. 98:503-517), northern hybridization (see, e.g., Freeman et al., 1983, Proc. Natl. Acad. Sci. USA 80:4094-4098), restriction endonuclease mapping (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, 2<sup>nd</sup> Ed. Cold Spring Harbor Laboratory Press, New York), RNase protection assays (Current Protocols in Molecular Biology, John Wiley and Sons, New York, 1997), DNA sequence analysis, and polymerase chain reaction amplification (PCR; U.S. Patent Nos. 4,683,202, 4,683,195, and 4,889,818; Gyllenstein et al., 1988, Proc. Natl. Acad. Sci. USA 85:7652-7657; Ochman et al., 1988, Genetics 120:621-623; Loh et al., 1989, Science 243:217-220) followed by Southern hybridization with probes specific for the component protein genes, in various cell types. Methods of amplification other than PCR commonly known in the art can be employed. In one embodiment, Southern hybridization can be used to detect genetic linkage of component protein gene mutations to physiological or pathological states. Various cell types, at various stages of development, can be characterized for their expression of component proteins at the same time and in the same cells. The stringency of the

hybridization conditions for northern or Southern blot analysis can be manipulated to ensure detection of nucleic acids with the desired degree of relatedness to the specific probes used. Modifications to these methods and other methods commonly known in the art can be used.

Derivatives (e.g., fragments), homologs and analogs of one component protein can be assayed for binding to another component protein in the same complex by any method known in the art, for example the modified yeast matrix mating test described in Section 4.6.1 *infra*, immunoprecipitation with an antibody that binds to the component protein complexed with other component proteins in the same complex, followed by size fractionation of the immunoprecipitated proteins (e.g., by denaturing or nondenaturing polyacrylamide gel electrophoresis), Western blot analysis, etc.

One embodiment of the invention provides a method for screening a derivative, homolog or analog of a component protein for biological activity comprising contacting said derivative, homolog or analog of the component protein with the other component proteins in the same complex; and detecting the formation of a complex between said derivative, homolog or analog of the component protein and the other component proteins; wherein detecting formation of said complex indicates that said derivative, homolog or analog of has biological (e.g., binding) activity.

The invention also provides methods of modulating the activity of a component protein that can participate in a protein complex by administration of a binding partner of that protein or derivative, homolog or analog thereof.

In a specific embodiment of the present invention, a protein complex of the present invention is administered to treat or prevent a disease or disorder, since the complex and/or component proteins have been implicated in the disease and disorder. Accordingly, a protein complex or a derivative, homolog, analog or fragment thereof, nucleic acids encoding the component proteins, anti-complex antibodies, and other modulators of protein complex activity, can be tested for activity in treating or preventing a disease or disorder in *in vitro* and *in vivo* assays.

In one embodiment, a therapeutic of the invention can be assayed for activity in treating or preventing a disease by contacting cultured cells that exhibit an indicator of the disease *in vitro*, with the therapeutic, and comparing the level of said indicator in the cells contacted with the therapeutic, with said level of said indicator in cells not so contacted, wherein a lower level in said contacted cells indicates that the therapeutic has activity in treating or preventing the disease.

In another embodiment of the invention, a therapeutic of the invention can be assayed for activity in treating or preventing a disease by administering the therapeutic to a test animal that is predisposed to develop symptoms of a disease, and measuring the change in said symptoms of the disease after administration of said therapeutic, wherein a reduction in the severity of the symptoms of the disease or prevention of the symptoms of the disease indicates that the therapeutic has activity in treating or preventing the disease. Such a test animal can be any one of a number of animal models known in the art for disease. These animal models are well known in the art. These animal models include, but are not limited to those which are listed in the section 4.6 (supra) as exemplary animal models to study any of the complexes provided in the invention.

#### 4.6 SCREENING FOR MODULATORS OF THE PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

A complex of the present invention, the component proteins of the complex and nucleic acids encoding the component proteins, as well as derivatives and fragments of the amino and nucleic acids, can be used to screen for compounds that bind to, or modulate the amount of, activity of, or protein component composition of, said complex, and thus, have potential use as modulators, i.e., agonists or antagonists, of complex activity, and/or complex formation, i.e., the amount of complex formed, and/or protein component composition of the complex.

Thus, the present invention is also directed to methods for screening for molecules that bind to, or modulate the function of, amount of, activity of, formation of or protein component composition of, a complex of the present invention. In one embodiment of the invention, the method for screening for a molecule that modulates directly or indirectly the function, activity or formation of a complex of the present invention comprises exposing said complex, or a cell or organism containing the complex machinery, to one or more candidate molecules under conditions conducive to modulation; and determining the amount of, the biochemical activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependend on the complex and/or the abundance and/or activity of a protein or protein complex dependend on the function of the complex and/or product of a gene dependend on the complex in the presence of the one or more candidate

molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene depend on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

In a further specific embodiment, a modulation of the formation process of a complex can be determined.

Such a modulation can either be a change in the typical time course of its formation or a change in the typical steps leading to the formation of the complete complex.

Such changes can for example be detected by analysing and comparing the process of complex formation in untreated wild type cells of a particular type and/or cells showing or having the predisposition to develop a certain disease phenotype and/or cells which have been treated with particular conditions and/or particular agents in a particular situation.

Methods to study such changes in time course are well known in the art and include for example Western-blot analysis of the proteins in the complex isolated at different steps of its formation.

Furthermore an aberrant intracellular localization of the protein complex and/or an aberrant transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or a gene dependent on the complex can serve as a marker for a disease and thus have diagnostic utility for any disease which is caused by an aberrant activity, function, composition or formation of the complex of the invention.

Methods to study the intracellular localization are well known in the art and include, but are not limited to immunofluorescence analysis using antibodies specific for components of the protein. Preferentially, double-stainings including staining of other cellular structures are being used to facilitate the detection of the intracellular localization. Methods to analyse the transcription levels of a gene dependent on the complex are also well known in the art and include Northern blot analysis, quantitative PCR etc. The abundance of proteins dependent on the protein can be analyzed as described supra. Methods to study changes in the activity of proteins dependent on complex depend on the protein. The choice of such methods will be apparent to any person skilled in the art.



In another embodiment, the present invention further relates to a process for the identification and/or preparation of an effector of the complex comprising the step of bringing into contact a product of any of claims 1 to 8 with a compound, a mixture or a library of compounds and determining whether the compound or a certain compound of the mixture or library binds to the product and/or effects the products biological activity and optionally further purifying the compound positively tested as effector.

In another embodiment, the present invention is directed to a method for screening for a molecule that binds a protein complex of the present invention comprising exposing said complex, or a cell or organism containing the complex machinery, to one or more candidate molecules; and determining whether said complex is bound by any of said candidate molecules. Such screening assays can be carried out using cell-free and cell-based methods that are commonly known in the art in vitro, in vivo or ex vivo. For example, an isolated complex can be employed, or a cell can be contacted with the candidate molecule and the complex can be isolated from such contacted cells and the isolated complex can be assayed for activity or component composition. In another example, a cell containing the complex can be contacted with the candidate molecule and the levels of the complex in the contacted cell can be measured. Additionally, such assays can be carried out in cells recombinantly expressing a component protein from the fourth column of table 1, or a functionally active fragment or functionally active derivative thereof, and a component protein from fifth column of table 1, or a functionally active fragment or functionally active derivative thereof. Additionally, such assays can also be carried out in cells recombinantly expressing all component proteins from the group of proteins in the fifth column of table 1.

For example, assays can be carried out using recombinant cells expressing the protein components of a complex, to screen for molecules that bind to, or interfere with, or promote complex activity or formation. In preferred embodiments, polypeptide derivatives that have superior stabilities but retain the ability to form a complex (e.g., one or more component proteins modified to be resistant to proteolytic degradation in the binding assay buffers, or to be resistant to oxidative degradation), are used to screen for modulators of complex activity or formation. Such resistant molecules can be generated, e.g., by substitution of amino acids at proteolytic cleavage sites, the use of chemically derivatized amino acids at proteolytic susceptible sites, and the replacement of amino acid residues subject to oxidation, i.e. methionine and cysteine.

A particular aspect of the present invention relates to identifying molecules that inhibit or promote formation or degradation of a complex of the present invention, e.g., using the method described for isolating the complex and identifying members of the complex using the TAP assay described in Section 4, *infra*, and in WO 00/09716 and Rigaut et al., 1999, *Nature Biotechnol.* 17:1030-1032, which are each incorporated by reference in their entirety. TNRF1

In another embodiment of the invention, a modulator is identified by administering a candidate molecule to a transgenic non-human animal expressing the complex component proteins from promoters that are not the native promoters of the respective proteins, more preferably where the candidate molecule is also recombinantly expressed in the transgenic non-human animal. Alternatively, the method for identifying such a modulator can be carried out *in vitro*, preferably with a purified complex, and a purified candidate molecule.

Agents/molecules (candidate molecules) to be screened can be provided as mixtures of a limited number of specified compounds, or as compound libraries, peptide libraries and the like. Agents/molecules to be screened may also include all forms of antisera, antisense nucleic acids, etc., that can modulate complex activity or formation. Exemplary candidate molecules and libraries for screening are set forth in Section 4.6.1, *infra*.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Patent No. 5,096,815, U.S. Patent No. 5,223,409, and U.S. Patent No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and International Patent Publication No. WO 94/18318.

In a specific embodiment, screening can be carried out by contacting the library members with a complex immobilized on a solid phase, and harvesting those library members that bind to the protein (or encoding nucleic acid or derivative). Examples of such screening methods, termed "panning" techniques, are described by way of example in Parmley and Smith, 1988, *Gene* 73:305-318; Fowlkes et al., 1992, *BioTechniques*

13:422-427; International Patent Publication No. WO 94/18318; and in references cited hereinabove.

In a specific embodiment, fragments and/or analogs of protein components of a complex, especially peptidomimetics, are screened for activity as competitive or non-competitive inhibitors of complex formation (amount of complex or composition of complex) or activity in the cell, which thereby inhibit complex activity or formation in the cell.

In one embodiment, agents that modulate (i.e., antagonize or agonize) complex activity or formation can be screened for using a binding inhibition assay, wherein agents are screened for their ability to modulate formation of a complex under aqueous, or physiological, binding conditions in which complex formation occurs in the absence of the agent to be tested. Agents that interfere with the formation of complexes of the invention are identified as antagonists of complex formation. Agents that promote the formation of complexes are identified as agonists of complex formation. Agents that completely block the formation of complexes are identified as inhibitors of complex formation.

Methods for screening may involve labeling the component proteins of the complex with radioligands (e.g.,  $^{125}\text{I}$  or  $^3\text{H}$ ), magnetic ligands (e.g., paramagnetic beads covalently attached to photobiotin acetate), fluorescent ligands (e.g., fluorescein or rhodamine), or enzyme ligands (e.g., luciferase or  $\beta$ -galactosidase). The reactants that bind in solution can then be isolated by one of many techniques known in the art, including but not restricted to, co-immunoprecipitation of the labeled complex moiety using antisera against the unlabeled binding partner (or labeled binding partner with a distinguishable marker from that used on the second labeled complex moiety), immunoaffinity chromatography, size exclusion chromatography, and gradient density centrifugation. In a preferred embodiment, the labeled binding partner is a small fragment or peptidomimetic that is not retained by a commercially available filter. Upon binding, the labeled species is then unable to pass through the filter, providing for a simple assay of complex formation.

Methods commonly known in the art are used to label at least one of the component members of the complex. Suitable labeling methods include, but are not limited to, radiolabeling by incorporation of radiolabeled amino acids, e.g.,  $^3\text{H}$ -leucine or  $^{35}\text{S}$ -methionine, radiolabeling by post-translational iodination with  $^{125}\text{I}$  or  $^{131}\text{I}$  using the chloramine T method, Bolton-Hunter reagents, etc., or labeling with  $^{32}\text{P}$  using phosphorylase and inorganic radiolabeled phosphorous, biotin labeling with photobiotin-

acetate and sunlamp exposure, etc. In cases where one of the members of the complex is immobilized, e.g., as described *infra*, the free species is labeled. Where neither of the interacting species is immobilized, each can be labeled with a distinguishable marker such that isolation of both moieties can be followed to provide for more accurate quantification, and to distinguish the formation of homomeric from heteromeric complexes. Methods that utilize accessory proteins that bind to one of the modified interactants to improve the sensitivity of detection, increase the stability of the complex, etc., are provided.

Typical binding conditions are, for example, but not by way of limitation, in an aqueous salt solution of 10-250 mM NaCl, 5-50 mM Tris-HCl, pH 5-8, and 0.5% Triton X-100 or other detergent that improves specificity of interaction. Metal chelators and/or divalent cations may be added to improve binding and/or reduce proteolysis. Reaction temperatures may include 4, 10, 15, 22, 25, 35, or 42 degrees Celsius, and time of incubation is typically at least 15 seconds, but longer times are preferred to allow binding equilibrium to occur. Particular complexes can be assayed using routine protein binding assays to determine optimal binding conditions for reproducible binding.

The physical parameters of complex formation can be analyzed by quantification of complex formation using assay methods specific for the label used, e.g., liquid scintillation counting for radioactivity detection, enzyme activity for enzyme-labeled moieties, etc. The reaction results are then analyzed utilizing Scatchard analysis, Hill analysis, and other methods commonly known in the arts (see, e.g., *Proteins, Structures, and Molecular Principles*, 2<sup>nd</sup> Edition (1993) Creighton, Ed., W.H. Freeman and Company, New York).

In a second common approach to binding assays, one of the binding species is immobilized on a filter, in a microtiter plate well, in a test tube, to a chromatography matrix, etc., either covalently or non-covalently. Proteins can be covalently immobilized using any method well known in the art, for example, but not limited to the method of Kadonaga and Tjian, 1986, *Proc. Natl. Acad. Sci. USA* 83:5889-5893, i.e., linkage to a cyanogen-bromide derivatized substrate such as CNBr-Sepharose 4B (Pharmacia). Where needed, the use of spacers can reduce steric hindrance by the substrate. Non-covalent attachment of proteins to a substrate include, but are not limited to, attachment of a protein to a charged surface, binding with specific antibodies, binding to a third unrelated interacting protein, etc.

Assays of agents (including cell extracts or a library pool) for competition for binding of one member of a complex (or derivatives thereof) with another member of the complex labeled by any means (e.g., those means described above) are provided to screen for competitors or enhancers of complex formation.

In specific embodiments, blocking agents to inhibit non-specific binding of reagents to other protein components, or absorptive losses of reagents to plastics, immobilization matrices, etc., are included in the assay mixture. Blocking agents include, but are not restricted to bovine serum albumin,  $\beta$ -casein, nonfat dried milk, Denhardt's reagent, Ficoll, polyvinylpyrrolidone, nonionic detergents (NP40, Triton X-100, Tween 20, Tween 80, etc.), ionic detergents (e.g., SDS, LDS, etc.), polyethylene glycol, etc. Appropriate blocking agent concentrations allow complex formation.

After binding is performed, unbound, labeled protein is removed in the supernatant, and the immobilized protein retaining any bound, labeled protein is washed extensively. The amount of bound label is then quantified using standard methods in the art to detect the label as described, *supra*.

In another specific embodiment screening for modulators of the protein complexes/protein as provided herein can be carried out by attaching those and/or the antibodies as provided herein to a solid carrier. In a further specific embodiment, the invention relates to an array of said molecules.

The preparation of such an array containing different types of proteins, including antibodies) is well known in the art and is apparent to a person skilled in the art (see e.g. Ekins et al., 1989, J. Pharm. Biomed. Anal. 7:155-168; Mitchell et al. 2002, Nature Biotechnol. 20:225-229; Petricoin et al., 2002, Lancet 359:572-577; Templin et al., 2001, Trends Biotechnol. 20:160-166; Wilson and Nock, 2001, Curr. Opin. Chem. Biol. 6:81-85; Lee et al., 2002 Science 295:1702-1705; MacBeath and Schreiber, 2000, Science 289:1760; Blawas and Reichert, 1998, Biomaterials 19:595; Kane et al., 1999, Biomaterials 20:2363; Chen et al., 1997, Science 276:1425; Vaughan et al., 1996, Nature Biotechnol. 14:309-314; Mahler et al., 1997, Immunotechnology 3:31-43; Roberts et al., 1999, Curr. Opin. Chem. Biol. 3:268-273; Nord et al., 1997, Nature Biotechnol. 15:772-777; Nord et al., 2001, Eur. J. Biochem. 268:4269-4277; Brody and Gold, 2000, Rev. Mol. Biotechnol. 74:5-13; Karlstroem and Nygren, 2001, Anal. Biochem. 295:22-30; Nelson et al., 2000, Electrophoresis 21:1155-1163; Honore et al., 2001, Expert Rev. Mol. Diagn. 3:265-274; Albala, 2001, Expert Rev. Mol. Diagn. 2:145-152, Figeys and Pinto, 2001, Electrophoresis 2:208-216 and references in the publications listed here).

Complexes can be attached to an array by different means as will be apparent to a person skilled in the art. Complexes can for example be added to the array via a TAP-tag (as described in WO/0009716 and in Rigaut et al., 1999, Nature Biotechnol. 10:1030-1032) after the purification step or by another suitable purification scheme as will be apparent to a person skilled in the art.

Optionally, the proteins of the complex can be cross-linked to enhance the stability of the complex. Different methods to cross-link proteins are well known in the art. Reactive end-groups of cross-linking agents include but are not limited to -COOH, -SH, -NH<sub>2</sub> or N-oxy-succinamate.

The spacer of the cross-linking agent should be chosen with respect to the size of the complex to be cross-linked. For small protein complexes, comprising only a few proteins, relatively short spacers are preferable in order to reduce the likelihood of cross-linking separate complexes in the reaction mixture. For larger protein complexes, additional use of larger spacers is preferable in order to facilitate cross-linking between proteins within the complex.

It is preferable to check the success-rate of cross-linking before linking the complex to the carrier.

As will be apparent to a person skilled in the art, the optimal rate of cross-linking need to be determined on a case by case basis. This can be achieved by methods well known in the art, some of which are exemplary described below.

A sufficient rate of cross-linking can be checked f.e. by analysing the cross-linked complex vs. a non-cross-linked complex on a denaturing protein gel.

If cross-linking has been performed successfully, the proteins of the complex are expected to be found in the same lane, whereas the proteins of the non-cross-linked complex are expected to be separated according to their individual characteristics. Optionally the presence of all proteins of the complex can be further checked by peptide-sequencing of proteins in the respective bands using methods well known in the art such as mass spectrometry and/or Edman degradation.

In addition, a rate of crosslinking which is too high should also be avoided. If cross-linking has been carried out too extensively, there will be an increasing amount of cross-linking of the individual protein complex, which potentially interferes with a screening for potential binding partners and/or modulators etc. using the arrays.

The presence of such structures can be determined by methods well known in the art and include e.g. gel-filtration experiments comparing the gel filtration profile solutions containing cross-linked complexes vs. uncross-linked complexes.

Optionally, functional assays as will be apparent to a person skilled in the art, some of which are exemplarily provided herein, can be performed to check the integrity of the complex.

Alternatively, members of the protein complex can be expressed as a single fusion protein and coupled to the matrix as will be apparent to a person skilled in the art.

Optionally, the attachment of the complex or proteins or antibody as outlined above can be further monitored by various methods apparent to a person skilled in the art. Those include, but are not limited to surface plasmon resonance (see e.g. McDonnel, 2001, *Curr. Opin. Chem. Biol.* 5:572-577; Lee, 2001, *Trends Biotechnol.* 19:217-222; Weinberger et al., 2000, 1:395-416; Pearson et al., 2000, *Ann. Clin. Biochem.* 37:119-145; Vely et al., 2000, *Methods Mol. Biol.* 121:313-321; Slepak, 2000, *J. Mol. Recognit.* 13:20-26.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the mDAB1-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the mDAB1-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the mDAB1-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the mDAB1-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the JIP1-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting



protein(s)) of the Fe65L2-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Fe65L2-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pilt/TJP4-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pilt/TJP4-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Pilt/TJP4-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pilt/TJP4-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting

proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Neurotrypsin-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Neurotrypsin-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Neurotrypsin-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Hunc18a-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Hunc18a-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Hunc18a-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Hunc18a-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Telencephalin-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Telencephalin-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Telencephalin-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Telencephalin-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PC7-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PC7-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting of the PC7-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PC7-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the VTRP-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the VTRP-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the VTRP-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the VTRP-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the

expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the BACE1 (new)-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the BACE2-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PALADIN-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PALADIN-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PALADIN-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the PALADIN-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the TFCEP2-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the p75 NTR-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting protein(s)) of the p75 NTR-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the p75 NTR-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the p75 NTR-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Lamezin-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Lamezin-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Lamezin-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Lamezin-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by

means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-C59-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BRI/ITM2B-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BRI/ITM2B-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the BRI/ITM2B-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BRI/ITM2B-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

#### 4.6.1 CANDIDATE MOLECULES

Any molecule known in the art can be tested for its ability to modulate (increase or decrease) the amount of, activity of, or protein component composition of a complex of the present invention as detected by a change in the amount of, activity of, or protein component composition of, said complex. By way of example, a change in the amount of the complex can be detected by detecting a change in the amount of the complex that can be isolated from a cell expressing the complex machinery. For identifying a molecule that modulates complex activity, candidate molecules can be directly provided



to a cell expressing the complex machinery, or, in the case of candidate proteins, can be provided by providing their encoding nucleic acids under conditions in which the nucleic acids are recombinantly expressed to produce the candidate proteins within the cell expressing the complex machinery, the complex is then isolated from the cell and the isolated complex is assayed for activity using methods well known in the art, not limited to those described, *supra*.

This embodiment of the invention is well suited to screen chemical libraries for molecules which modulate, e.g., inhibit, antagonize, or agonize, the amount of, activity of, or protein component composition of the complex. The chemical libraries can be peptide libraries, peptidomimetic libraries, chemically synthesized libraries, recombinant, e.g., phage display libraries, and in vitro translation-based libraries, other non-peptide synthetic organic libraries, etc.

Exemplary libraries are commercially available from several sources (ArQule, Tripos/PanLabs, ChemDesign, Pharmacopoeia). In some cases, these chemical libraries are generated using combinatorial strategies that encode the identity of each member of the library on a substrate to which the member compound is attached, thus allowing direct and immediate identification of a molecule that is an effective modulator. Thus, in many combinatorial approaches, the position on a plate of a compound specifies that compound's composition. Also, in one example, a single plate position may have from 1-20 chemicals that can be screened by administration to a well containing the interactions of interest. Thus, if modulation is detected, smaller and smaller pools of interacting pairs can be assayed for the modulation activity. By such methods, many candidate molecules can be screened.

Many diversity libraries suitable for use are known in the art and can be used to provide compounds to be tested according to the present invention. Alternatively, libraries can be constructed using standard methods. Chemical (synthetic) libraries, recombinant expression libraries, or polysome-based libraries are exemplary types of libraries that can be used.

The libraries can be constrained or semirigid (having some degree of structural rigidity), or linear or nonconstrained. The library can be a cDNA or genomic expression library, random peptide expression library or a chemically synthesized random peptide library, or non-peptide library. Expression libraries are introduced into the cells in which the assay occurs, where the nucleic acids of the library are expressed to produce their encoded proteins.

In one embodiment, peptide libraries that can be used in the present invention may be libraries that are chemically synthesized *in vitro*. Examples of such libraries are given in Houghten et al., 1991, *Nature* 354:84-86, which describes mixtures of free hexapeptides in which the first and second residues in each peptide were individually and specifically defined; Lam et al., 1991, *Nature* 354:82-84, which describes a "one bead, one peptide" approach in which a solid phase split synthesis scheme produced a library of peptides in which each bead in the collection had immobilized thereon a single, random sequence of amino acid residues; Medynski, 1994, *Bio/Technology* 12:709-710, which describes split synthesis and T-bag synthesis methods; and Gallop et al., 1994, *J. Med. Chem.* 37:1233-1251. Simply by way of other examples, a combinatorial library may be prepared for use, according to the methods of Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; or Salmon et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712. PCT Publication No. WO 93/20242 and Brenner and Lerner, 1992, *Proc. Natl. Acad. Sci. USA* 89:5381-5383 describe "encoded combinatorial chemical libraries," that contain oligonucleotide identifiers for each chemical polymer library member.

In a preferred embodiment, the library screened is a biological expression library that is a random peptide phage display library, where the random peptides are constrained (e.g., by virtue of having disulfide bonding).

Further, more general, structurally constrained, organic diversity (e.g., nonpeptide) libraries, can also be used. By way of example, a benzodiazepine library (see e.g., Bunin et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:4708-4712) may be used.

Conformationally constrained libraries that can be used include but are not limited to those containing invariant cysteine residues which, in an oxidizing environment, cross-link by disulfide bonds to form cystines, modified peptides (e.g., incorporating fluorine, metals, isotopic labels, are phosphorylated, etc.), peptides containing one or more non-naturally occurring amino acids, non-peptide structures, and peptides containing a significant fraction of  $\gamma$ -carboxyglutamic acid.

Libraries of non-peptides, e.g., peptide derivatives (for example, that contain one or more non-naturally occurring amino acids) can also be used. One example of these are peptoid libraries (Simon et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:9367-9371). Peptoids are polymers of non-natural amino acids that have naturally occurring side

chains attached not to the  $\alpha$  carbon but to the backbone amino nitrogen. Since peptoids are not easily degraded by human digestive enzymes, they are advantageously more easily adaptable to drug use. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11138-11142).

The members of the peptide libraries that can be screened according to the invention are not limited to containing the 20 naturally occurring amino acids. In particular, chemically synthesized libraries and polysome based libraries allow the use of amino acids in addition to the 20 naturally occurring amino acids (by their inclusion in the precursor pool of amino acids used in library production). In specific embodiments, the library members contain one or more non-natural or non-classical amino acids or cyclic peptides. Non-classical amino acids include but are not limited to the D-isomers of the common amino acids,  $\gamma$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid;  $\gamma$ -Abu,  $\gamma$ -Ahx, 6-amino hexanoic acid; Aib, 2-amino isobutyric acid; 3-amino propionic acid; ornithine; norleucine; norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, designer amino acids such as  $\beta$ -methyl amino acids,  $\gamma$ -methyl amino acids, N-methyl amino acids, fluoro-amino acids and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

In a specific embodiment, fragments and/or analogs of complexes of the invention, or protein components thereof, especially peptidomimetics, are screened for activity as competitive or non-competitive inhibitors of complex activity or formation.

In another embodiment of the present invention, combinatorial chemistry can be used to identify modulators of the complexes. Combinatorial chemistry is capable of creating libraries containing hundreds of thousands of compounds, many of which may be structurally similar. While high throughput screening programs are capable of screening these vast libraries for affinity for known targets, new approaches have been developed that achieve libraries of smaller dimension but which provide maximum chemical diversity. (See e.g., Matter, 1997, *J. Med. Chem.* 40:1219-1229).

One method of combinatorial chemistry, affinity fingerprinting, has previously been used to test a discrete library of small molecules for binding affinities for a defined panel of proteins. The fingerprints obtained by the screen are used to predict the affinity of the individual library members for other proteins or receptors of interest (in the instant

invention, the protein complexes of the present invention and protein components thereof.) The fingerprints are compared with fingerprints obtained from other compounds known to react with the protein of interest to predict whether the library compound might similarly react. For example, rather than testing every ligand in a large library for interaction with a complex or protein component, only those ligands having a fingerprint similar to other compounds known to have that activity could be tested. (See, e.g., Kauvar et al., 1995, Chem. Biol. 2:107-118; Kauvar, 1995, Affinity fingerprinting, Pharmaceutical Manufacturing International. 8:25-28; and Kauvar, Toxic-Chemical Detection by Pattern Recognition in New Frontiers in Agrochemical Immunoassay, Kurtz, Stanker and Skeritt (eds), 1995, AOAC: Washington, D.C., 305-312).

Kay et al. (1993, Gene 128:59-65) disclosed a method of constructing peptide libraries that encode peptides of totally random sequence that are longer than those of any prior conventional libraries. The libraries disclosed in Kay et al. encode totally synthetic random peptides of greater than about 20 amino acids in length. Such libraries can be advantageously screened to identify complex modulators. (See also U.S. Patent No. 5,498,538 dated March 12, 1996; and PCT Publication No. WO 94/18318 dated August 18, 1994).

A comprehensive review of various types of peptide libraries can be found in Gallop et al., 1994, J. Med. Chem. 37:1233-1251.

#### 4.7 PHARMACEUTICAL COMPOSITIONS AND THERAPEUTIC/PROPHYLACTIC ADMINISTRATION

The invention provides methods of treatment (and prophylaxis) by administration to a subject of an effective amount of a therapeutic of the invention. In a preferred aspect, the therapeutic is substantially purified. The subject is preferably an animal including, but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human. In a specific embodiment, a non-human mammal is the subject.

Various delivery systems are known and can be used to administer a therapeutic of the invention, e.g., encapsulation in liposomes, microparticles, and microcapsules; use of recombinant cells capable of expressing the therapeutic, use of receptor-mediated endocytosis (e.g., Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432); construction of a

therapeutic nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds may be administered by any convenient route, for example by infusion, by bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral, rectal and intestinal mucosa, etc.), and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of a malignant tumor or neoplastic or pre-neoplastic tissue.

In another embodiment, the therapeutic can be delivered in a vesicle, in particular a liposome (Langer, 1990, *Science* 249:1527-1533; Treat et al., 1989, In: *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler, eds., Liss, New York, pp. 353-365; Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the therapeutic can be delivered via a controlled release system. In one embodiment, a pump may be used (Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201-240; Buchwald et al., 1980, *Surgery* 88:507-516; Saudek et al., 1989, *N. Engl. J. Med.* 321:574-579). In another embodiment, polymeric materials can be used (*Medical Applications of Controlled Release*, Langer and Wise, eds., CRC Press, Boca Raton, Florida, 1974; *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball, eds., Wiley, New York, 1984; Ranger and Peppas, 1983, *Macromol. Sci. Rev. Macromol. Chem.* 23:61; Levy et al., 1985, *Science* 228:190-192; During et al., 1989, *Ann. Neurol.* 25:351-356; Howard et al.,

1989, J. Neurosurg. 71:858-863). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (e.g., Goodson, 1984, In: Medical Applications of Controlled Release, supra, Vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer (1990, Science 249:1527-1533).

In a specific embodiment where the therapeutic is a nucleic acid encoding a protein therapeutic, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or by coating it with lipids, cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (e.g., Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid therapeutic can be introduced intracellularly and incorporated by homologous recombination within host cell DNA for expression.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a therapeutic, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH

buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated, in accordance with routine procedures, as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water or saline for injection can be provided so that the ingredients may be mixed prior to administration.

The therapeutics of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free carboxyl groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., those formed with free amine groups such as those derived from isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc., and those derived from sodium, potassium, ammonium, calcium, and ferric hydroxides, etc.

The amount of the therapeutic of the invention which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise

dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, suitable dosage ranges for intravenous administration are generally about 20-500 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

Suppositories generally contain active ingredient in the range of 0.5% to 10% by weight; oral formulations preferably contain 10% to 95% active ingredient.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. For example, the kit can comprise in one or more containers a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of proteins listed in the fourth column of table 1; and a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins listed in the fifth column of table 1.

Alternatively, the kit can comprise in one or more containers, all proteins, functionally active fragments or functionally active derivatives thereof of from the group of proteins in the sixth column of table 1.

The kits of the present invention can also contain expression vectors encoding the essential components of the complex machinery, which components after being expressed can be reconstituted in order to form a biologically active complex. Such a kit preferably also contains the required buffers and reagents. Optionally associated with such container(s) can be instructions for use of the kit and/or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of



pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

#### 4.8 ANIMAL MODELS

The present invention also provides animal models. In one embodiment, animal models for diseases and disorders involving the protein complexes of the present invention are provided. These animal models are well known in the art. These animal models include, but are not limited to those which are listed in the section 4.6 (supra) as exemplary animal models to study any of the complexes provided in the invention. Such animals can be initially produced by promoting homologous recombination or insertional mutagenesis between genes encoding the protein components of the complexes in the chromosome, and exogenous genes encoding the protein components of the complexes that have been rendered biologically inactive or deleted (preferably by insertion of a heterologous sequence, e.g., an antibiotic resistance gene). In a preferred aspect, homologous recombination is carried out by transforming embryo-derived stem (ES) cells with one or more vectors containing one or more insertionally inactivated genes, such that homologous recombination occurs, followed by injecting the transformed ES cells into a blastocyst, and implanting the blastocyst into a foster mother, followed by the birth of the chimeric animal ("knockout animal") in which a gene encoding a component protein from the fourth column of table 1, or a functionally active fragment or functionally active derivative thereof, and a gene encoding a component protein from the fifth column of table 1, or a functionally active fragment or functionally active derivative thereof, has been inactivated or deleted (Capecchi, 1989, Science 244:1288-1292).

In another preferred aspect, homologous recombination is carried out by transforming embryo-derived stem (ES) cells with one or more vectors containing one or more insertionally inactivated genes, such that homologous recombination occurs, followed by injecting the transformed ES cells into a blastocyst, and implanting the blastocyst into a foster mother, followed by the birth of the chimeric animal ("knockout animal") in which the genes of all component proteins from the group of proteins listed in the fourth column of table 1 or of all proteins from the group of proteins listed in the fifth column of table 1 have been inactivated or deleted.

The chimeric animal can be bred to produce additional knockout animals. Such animals can be mice, hamsters, sheep, pigs, cattle, etc., and are preferably non-human mammals. In a specific embodiment, a knockout mouse is produced.

Such knockout animals are expected to develop, or be predisposed to developing, diseases or disorders associated with mutations involving the protein complexes of the present invention, and thus, can have use as animal models of such diseases and disorders, e.g., to screen for or test molecules (e.g., potential therapeutics) for such diseases and disorders.

In a different embodiment of the invention, transgenic animals that have incorporated and express (or over-express or mis-express) a functional gene encoding a protein component of the complex, e.g. by introducing the a gene encoding one or more of the components of the complex under the control of a heterologous promoter (i.e., a promoter that is not the native promoter of the gene) that either over-expresses the protein or proteins, or expresses them in tissues not normally expressing the complexes or proteins, can have use as animal models of diseases and disorders characterized by elevated levels of the protein complexes. Such animals can be used to screen or test molecules for the ability to treat or prevent the diseases and disorders cited supra.

In one embodiment, the present invention provides a recombinant non-human animal in which an endogenous gene encoding a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group of proteins listed in the fourth column of table 1, and an endogenous gene encoding a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins listed in the fifth column of table 1 has been deleted or inactivated by homologous recombination or insertional mutagenesis of said animal or an ancestor thereof. In addition, the present invention provides a recombinant non-human animal in which the endogenous genes of all proteins, or functionally active fragments or functionally active derivatives thereof of one of the group of proteins listed in the sixth column have been deleted or inactivated by homologous recombination or insertional mutagenesis of said animal or an ancestor thereof:

In another embodiment, the present invention provides a recombinant non-human animal in which an endogenous gene encoding a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of proteins of the fourth column of table 1, and an endogenous gene

encoding a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins of the fifth column, of table 1 are recombinantly expressed in said animal or an ancestor thereof.

The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

## EXAMPLES

An object of the present invention was to identify protein complexes of the APP processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said complexes were identified. The components are listed in table 1.

APP-C59-complex, Bace1-complex, Bace2-complex, BRI-complex, mDab1-complex, Fe65L2-complex, Plit-complex, Paladin-complex, Neurotrypsin-complex, Hunc18a-complex, Telencephalin-complex, PC7-complex, TFCP2-complex, Jip1-complex, Lamezin-complex, VTRP-complex, p75-NTR-complex

Said object is further achieved by the characterization of component proteins. These proteins are listed in table 2.

Thus, the invention relates to the following embodiments:

The invention relates to the following embodiments of the mDab1-complex

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "APLP1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a

nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "ApoE receptor 2" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ApoE receptor 2" encoded by a nucleic acid that hybridizes to the "ApoE receptor 2" nucleic acid or its complement under low stringency conditions,

(v) "DAB1 " (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1 " encoded by a nucleic acid that hybridizes to the "DAB1 " nucleic acid or its complement under low stringency conditions, and

(vi) "VLDL receptor" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLDL receptor" encoded by a nucleic acid that hybridizes to the "VLDL receptor" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "ACE" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACE" encoded by a nucleic acid that hybridizes to the "ACE" nucleic acid or its complement under low stringency conditions,

(ii) "APG-1" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APG-1" encoded by a nucleic acid that hybridizes to the "APG-1" nucleic acid or its complement under low stringency conditions,

(iii) "Archvillin" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Archvillin" encoded by a

nucleic acid that hybridizes to the "Archvillin" nucleic acid or its complement under low stringency conditions,

(iv) "CRK" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,

(v) "CRKL" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRKL" encoded by a nucleic acid that hybridizes to the "CRKL" nucleic acid or its complement under low stringency conditions,

(vi) "CSNK1D" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1D" encoded by a nucleic acid that hybridizes to the "CSNK1D" nucleic acid or its complement under low stringency conditions,

(vii) "CSNK1E" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1E" encoded by a nucleic acid that hybridizes to the "CSNK1E" nucleic acid or its complement under low stringency conditions,

(viii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,

(ix) "DAB2IP" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(x) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions,

(xi) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the

"Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions,

(xii) "ISL1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISL1" encoded by a nucleic acid that hybridizes to the "ISL1" nucleic acid or its complement under low stringency conditions,

(xiii) "ITGA1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGA1" encoded by a nucleic acid that hybridizes to the "ITGA1" nucleic acid or its complement under low stringency conditions,

(xiv) "ITGB1" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGB1" encoded by a nucleic acid that hybridizes to the "ITGB1" nucleic acid or its complement under low stringency conditions,

(xv) "LDLR" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LDLR" encoded by a nucleic acid that hybridizes to the "LDLR" nucleic acid or its complement under low stringency conditions,

(xvi) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions,

(xvii) "NEDD5" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD5" encoded by a nucleic acid that hybridizes to the "NEDD5" nucleic acid or its complement under low stringency conditions,

(xviii) "PLK" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLK" encoded by a nucleic acid that hybridizes to the "PLK" nucleic acid or its complement under low stringency conditions,

(xix) "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" encoded by a nucleic acid that hybridizes to the "Proto-

oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" nucleic acid or its complement under low stringency conditions,

(xx) "QPRT" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "QPRT" encoded by a nucleic acid that hybridizes to the "QPRT" nucleic acid or its complement under low stringency conditions,

(xxi) "S-100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S-100 beta" encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions,

(xxii) "SIM TO PLEXIN 1 - MOUSE" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO PLEXIN 1 - MOUSE" encoded by a nucleic acid that hybridizes to the "SIM TO PLEXIN 1 - MOUSE" nucleic acid or its complement under low stringency conditions,

(xxiii) "TGM5" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TGM5" encoded by a nucleic acid that hybridizes to the "TGM5" nucleic acid or its complement under low stringency conditions, and

(xxiv) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Dab1 (SEQ ID NO. 13), or a functionally active derivative thereof, or a functionally active

fragment thereof, or a homolog thereof, or a variant of 'Dab1' encoded by a nucleic acid that hybridizes to the 'Dab1' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "ACE" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACE" encoded by a nucleic acid that hybridizes to the "ACE" nucleic acid or its complement under low stringency conditions,
- (ii) "APG-1" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APG-1" encoded by a nucleic acid that hybridizes to the "APG-1" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iv) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "ApoE receptor 2" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ApoE receptor 2" encoded by a nucleic acid that hybridizes to the "ApoE receptor 2" nucleic acid or its complement under low stringency conditions,
- (vii) "Archvillin" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Archvillin" encoded by a nucleic acid that hybridizes to the "Archvillin" nucleic acid or its complement under low stringency conditions,



- (viii) "CRK" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,
- (ix) "CRKL" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRKL" encoded by a nucleic acid that hybridizes to the "CRKL" nucleic acid or its complement under low stringency conditions,
- (x) "CSNK1D" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1D" encoded by a nucleic acid that hybridizes to the "CSNK1D" nucleic acid or its complement under low stringency conditions,
- (xi) "CSNK1E" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1E" encoded by a nucleic acid that hybridizes to the "CSNK1E" nucleic acid or its complement under low stringency conditions,
- (xii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (xiii) "DAB1 " (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1 " encoded by a nucleic acid that hybridizes to the "DAB1 " nucleic acid or its complement under low stringency conditions,
- (xiv) "DAB2IP" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,
- (xv) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions,
- (xvi) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions,

(xvii) "ISL1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISL1" encoded by a nucleic acid that hybridizes to the "ISL1" nucleic acid or its complement under low stringency conditions,

(xviii) "ITGA1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGA1" encoded by a nucleic acid that hybridizes to the "ITGA1" nucleic acid or its complement under low stringency conditions,

(xix) "ITGB1" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGB1" encoded by a nucleic acid that hybridizes to the "ITGB1" nucleic acid or its complement under low stringency conditions,

(xx) "LDLR" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LDLR" encoded by a nucleic acid that hybridizes to the "LDLR" nucleic acid or its complement under low stringency conditions,

(xxi) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions,

(xxii) "NEDD5" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD5" encoded by a nucleic acid that hybridizes to the "NEDD5" nucleic acid or its complement under low stringency conditions,

(xxiii) "PLK" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLK" encoded by a nucleic acid that hybridizes to the "PLK" nucleic acid or its complement under low stringency conditions,

(xxiv) "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Proto-oncogene tyrosine kinase FYN (P59-

FYN, SYN, SLK) isoform 1" encoded by a nucleic acid that hybridizes to the "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" nucleic acid or its complement under low stringency conditions,

(xxv) "QPRT" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "QPRT" encoded by a nucleic acid that hybridizes to the "QPRT" nucleic acid or its complement under low stringency conditions,

(xxvi) "S-100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S-100 beta" encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions,

(xxvii) "SIM TO PLEXIN 1 - MOUSE" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO PLEXIN 1 - MOUSE" encoded by a nucleic acid that hybridizes to the "SIM TO PLEXIN 1 - MOUSE" nucleic acid or its complement under low stringency conditions,

(xxviii) "TGM5" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TGM5" encoded by a nucleic acid that hybridizes to the "TGM5" nucleic acid or its complement under low stringency conditions,

(xxix) "VLDL receptor" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLDL receptor" encoded by a nucleic acid that hybridizes to the "VLDL receptor" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions,

and a protein complex selected from complex (II) and comprising the following proteins:

(i) "ACE" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACE" encoded by a nucleic acid that hybridizes to the "ACE" nucleic acid or its complement under low stringency conditions,

- (ii) "APG-1" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APG-1" encoded by a nucleic acid that hybridizes to the "APG-1" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iv) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "Archvillin" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Archvillin" encoded by a nucleic acid that hybridizes to the "Archvillin" nucleic acid or its complement under low stringency conditions,
- (vii) "CRK" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,
- (viii) "CRKL" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRKL" encoded by a nucleic acid that hybridizes to the "CRKL" nucleic acid or its complement under low stringency conditions,
- (ix) "CSNK1D" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1D" encoded by a nucleic acid that hybridizes to the "CSNK1D" nucleic acid or its complement under low stringency conditions,
- (x) "CSNK1E" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1E" encoded by a

nucleic acid that hybridizes to the "CSNK1E" nucleic acid or its complement under low stringency conditions,

(xi) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,

(xii) "DAB1 " (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1 " encoded by a nucleic acid that hybridizes to the "DAB1 " nucleic acid or its complement under low stringency conditions,

(xiii) "DAB2IP" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(xiv) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions,

(xv) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions,

(xvi) "ISL1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISL1" encoded by a nucleic acid that hybridizes to the "ISL1" nucleic acid or its complement under low stringency conditions,

(xvii) "ITGA1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGA1" encoded by a nucleic acid that hybridizes to the "ITGA1" nucleic acid or its complement under low stringency conditions,

(xviii) "ITGB1" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGB1" encoded by a

nucleic acid that hybridizes to the "ITGB1" nucleic acid or its complement under low stringency conditions,

(xix) "LDLR" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LDLR" encoded by a nucleic acid that hybridizes to the "LDLR" nucleic acid or its complement under low stringency conditions,

(xx) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions,

(xxi) "NEDD5" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD5" encoded by a nucleic acid that hybridizes to the "NEDD5" nucleic acid or its complement under low stringency conditions,

(xxii) "PLK" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLK" encoded by a nucleic acid that hybridizes to the "PLK" nucleic acid or its complement under low stringency conditions,

(xxiii) "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" encoded by a nucleic acid that hybridizes to the "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" nucleic acid or its complement under low stringency conditions,

(xxiv) "QPRT" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "QPRT" encoded by a nucleic acid that hybridizes to the "QPRT" nucleic acid or its complement under low stringency conditions,

(xxv) "S-100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S-100 beta" encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions,

(xxvi) "SIM TO PLEXIN 1 - MOUSE" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"SIM TO PLEXIN 1 - MOUSE" encoded by a nucleic acid that hybridizes to the "SIM TO PLEXIN 1 - MOUSE" nucleic acid or its complement under low stringency conditions, (xxvii) "TGM5" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TGM5" encoded by a nucleic acid that hybridizes to the "TGM5" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 23 of the following proteins:

(i) "ACE" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACE" encoded by a nucleic acid that hybridizes to the "ACE" nucleic acid or its complement under low stringency conditions,

(ii) "APG-1" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APG-1" encoded by a nucleic acid that hybridizes to the "APG-1" nucleic acid or its complement under low stringency conditions,

(iii) "APLP1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iv) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

- (vi) "ApoE receptor 2" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ApoE receptor 2" encoded by a nucleic acid that hybridizes to the "ApoE receptor 2" nucleic acid or its complement under low stringency conditions,
- (vii) "Archvillin" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Archvillin" encoded by a nucleic acid that hybridizes to the "Archvillin" nucleic acid or its complement under low stringency conditions,
- (viii) "CRK" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,
- (ix) "CRKL" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRKL" encoded by a nucleic acid that hybridizes to the "CRKL" nucleic acid or its complement under low stringency conditions,
- (x) "CSNK1D" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1D" encoded by a nucleic acid that hybridizes to the "CSNK1D" nucleic acid or its complement under low stringency conditions,
- (xi) "CSNK1E" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1E" encoded by a nucleic acid that hybridizes to the "CSNK1E" nucleic acid or its complement under low stringency conditions,
- (xii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (xiii) "DAB1 " (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1 " encoded by a nucleic acid that hybridizes to the "DAB1 " nucleic acid or its complement under low stringency conditions,
- (xiv) "DAB2IP" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a



nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(xv) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions,

(xvi) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions,

(xvii) "ISL1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISL1" encoded by a nucleic acid that hybridizes to the "ISL1" nucleic acid or its complement under low stringency conditions,

(xviii) "ITGA1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGA1" encoded by a nucleic acid that hybridizes to the "ITGA1" nucleic acid or its complement under low stringency conditions,

(xix) "ITGB1" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGB1" encoded by a nucleic acid that hybridizes to the "ITGB1" nucleic acid or its complement under low stringency conditions,

(xx) "LDLR" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LDLR" encoded by a nucleic acid that hybridizes to the "LDLR" nucleic acid or its complement under low stringency conditions,

(xxi) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions,

(xxii) "NEDD5" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD5"

encoded by a nucleic acid that hybridizes to the "NEDD5" nucleic acid or its complement under low stringency conditions,

(xxiii) "PLK" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLK" encoded by a nucleic acid that hybridizes to the "PLK" nucleic acid or its complement under low stringency conditions,

(xxiv) "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" encoded by a nucleic acid that hybridizes to the "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" nucleic acid or its complement under low stringency conditions,

(xxv) "QPRT" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "QPRT" encoded by a nucleic acid that hybridizes to the "QPRT" nucleic acid or its complement under low stringency conditions,

(xxvi) "S-100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S-100 beta" encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions,

(xxvii) "SIM TO PLEXIN 1 - MOUSE" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO PLEXIN 1 - MOUSE" encoded by a nucleic acid that hybridizes to the "SIM TO PLEXIN 1 - MOUSE" nucleic acid or its complement under low stringency conditions,

(xxviii) "TGM5" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TGM5" encoded by a nucleic acid that hybridizes to the "TGM5" nucleic acid or its complement under low stringency conditions,

(xxix) "VLDL receptor" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLDL receptor" encoded by a nucleic acid that hybridizes to the "VLDL receptor" nucleic acid or its complement under low stringency conditions,

(xxx) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is

attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Dab1 complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the Dab1 complex selected from

(i) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions,

(ii) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions, and

(iii) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.
15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or  
(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.
18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;
21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.
22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions,
  - (ii) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.
24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease;

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions,

(ii) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions, and/or

(iii) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determinig whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing Dab1 complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a

protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "ACE" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACE" encoded by a nucleic acid that hybridizes to the "ACE" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APG-1" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APG-1" encoded by a nucleic acid that hybridizes to the "APG-1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APLP1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or



- (v) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "ApoE receptor 2" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ApoE receptor 2" encoded by a nucleic acid that hybridizes to the "ApoE receptor 2" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Archvillin" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Archvillin" encoded by a nucleic acid that hybridizes to the "Archvillin" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CRK" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CRKL" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRKL" encoded by a nucleic acid that hybridizes to the "CRKL" nucleic acid or its complement under low stringency conditions, and/or
- (x) "CSNK1D" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1D" encoded by a nucleic acid that hybridizes to the "CSNK1D" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "CSNK1E" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1E" encoded by a nucleic acid that hybridizes to the "CSNK1E" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "DAB1 " (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1 " encoded by a

nucleic acid that hybridizes to the "DAB1 " nucleic acid or its complement under low stringency conditions, and/or

(xiv) "DAB2IP" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions, and/or

(xv) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "ISL1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISL1" encoded by a nucleic acid that hybridizes to the "ISL1" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "ITGA1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGA1" encoded by a nucleic acid that hybridizes to the "ITGA1" nucleic acid or its complement under low stringency conditions, and/or

(xix) "ITGB1" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGB1" encoded by a nucleic acid that hybridizes to the "ITGB1" nucleic acid or its complement under low stringency conditions, and/or

(xx) "LDLR" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LDLR" encoded by a nucleic acid that hybridizes to the "LDLR" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "NEDD5" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD5" encoded by a nucleic acid that hybridizes to the "NEDD5" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "PLK" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLK" encoded by a nucleic acid that hybridizes to the "PLK" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" encoded by a nucleic acid that hybridizes to the "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "QPRT" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "QPRT" encoded by a nucleic acid that hybridizes to the "QPRT" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "S-100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S-100 beta" encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "SIM TO PLEXIN 1 - MOUSE" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO PLEXIN 1 - MOUSE" encoded by a nucleic acid that hybridizes to the "SIM TO PLEXIN 1 - MOUSE" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "TGM5" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TGM5" encoded by a nucleic acid that hybridizes to the "TGM5" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "VLDL receptor" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLDL receptor" encoded by a nucleic acid that hybridizes to the "VLDL receptor" nucleic acid or its complement under low stringency conditions, and/or  
(xxx) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not

having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "ACE" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACE" encoded by a nucleic acid that hybridizes to the "ACE" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APG-1" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APG-1" encoded by a nucleic acid that hybridizes to the "APG-1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APLP1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

- (v) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "ApoE receptor 2" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ApoE receptor 2" encoded by a nucleic acid that hybridizes to the "ApoE receptor 2" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Archvillin" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Archvillin" encoded by a nucleic acid that hybridizes to the "Archvillin" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CRK" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CRKL" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRKL" encoded by a nucleic acid that hybridizes to the "CRKL" nucleic acid or its complement under low stringency conditions, and/or
- (x) "CSNK1D" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1D" encoded by a nucleic acid that hybridizes to the "CSNK1D" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "CSNK1E" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1E" encoded by a nucleic acid that hybridizes to the "CSNK1E" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "DAB1 " (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1 " encoded by a

nucleic acid that hybridizes to the "DAB1 " nucleic acid or its complement under low stringency conditions, and/or

(xiv) "DAB2IP" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions, and/or

(xv) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "ISL1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISL1" encoded by a nucleic acid that hybridizes to the "ISL1" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "ITGA1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGA1" encoded by a nucleic acid that hybridizes to the "ITGA1" nucleic acid or its complement under low stringency conditions, and/or

(xix) "ITGB1" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGB1" encoded by a nucleic acid that hybridizes to the "ITGB1" nucleic acid or its complement under low stringency conditions, and/or

(xx) "LDLR" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LDLR" encoded by a nucleic acid that hybridizes to the "LDLR" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "NEDD5" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD5" encoded by a nucleic acid that hybridizes to the "NEDD5" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "PLK" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLK" encoded by a nucleic acid that hybridizes to the "PLK" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" encoded by a nucleic acid that hybridizes to the "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "QPRT" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "QPRT" encoded by a nucleic acid that hybridizes to the "QPRT" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "S-100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S-100 beta" encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "SIM TO PLEXIN 1 - MOUSE" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO PLEXIN 1 - MOUSE" encoded by a nucleic acid that hybridizes to the "SIM TO PLEXIN 1 - MOUSE" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "TGM5" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TGM5" encoded by a nucleic acid that hybridizes to the "TGM5" nucleic acid or its complement under low stringency conditions, and/or



(xxix) "VLDL receptor" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLDL receptor" encoded by a nucleic acid that hybridizes to the "VLDL receptor" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42 , wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "ACE" (SEQ ID No:1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACE" encoded by a nucleic acid that hybridizes to the "ACE" nucleic acid or its complement under low stringency conditions,

(ii) "APG-1" (SEQ ID No:2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APG-1" encoded by a nucleic acid that hybridizes to the "APG-1" nucleic acid or its complement under low stringency conditions,

(iii) "APLP1" (SEQ ID No:3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iv) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "ApoE receptor 2" (SEQ ID No:6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ApoE receptor 2" encoded by a nucleic acid that hybridizes to the "ApoE receptor 2" nucleic acid or its complement under low stringency conditions,

(vii) "Archvillin" (SEQ ID No:7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Archvillin" encoded by a nucleic acid that hybridizes to the "Archvillin" nucleic acid or its complement under low stringency conditions,

- (viii) "CRK" (SEQ ID No:8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,
- (ix) "CRKL" (SEQ ID No:9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRKL" encoded by a nucleic acid that hybridizes to the "CRKL" nucleic acid or its complement under low stringency conditions,
- (x) "CSNK1D" (SEQ ID No:10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1D" encoded by a nucleic acid that hybridizes to the "CSNK1D" nucleic acid or its complement under low stringency conditions,
- (xi) "CSNK1E" (SEQ ID No:11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSNK1E" encoded by a nucleic acid that hybridizes to the "CSNK1E" nucleic acid or its complement under low stringency conditions,
- (xii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (xiii) "DAB1 " (SEQ ID No:13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1 " encoded by a nucleic acid that hybridizes to the "DAB1 " nucleic acid or its complement under low stringency conditions,
- (xiv) "DAB2IP" (SEQ ID No:14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,
- (xv) "DNAJB1" (SEQ ID No:15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJB1" encoded by a nucleic acid that hybridizes to the "DNAJB1" nucleic acid or its complement under low stringency conditions,
- (xvi) "Hypothetical protein FLJ31432" (SEQ ID No:16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"Hypothetical protein FLJ31432" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ31432" nucleic acid or its complement under low stringency conditions,

(xvii) "ISL1" (SEQ ID No:17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISL1" encoded by a nucleic acid that hybridizes to the "ISL1" nucleic acid or its complement under low stringency conditions,

(xviii) "ITGA1" (SEQ ID No:18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGA1" encoded by a nucleic acid that hybridizes to the "ITGA1" nucleic acid or its complement under low stringency conditions,

(xix) "ITGB1" (SEQ ID No:19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGB1" encoded by a nucleic acid that hybridizes to the "ITGB1" nucleic acid or its complement under low stringency conditions,

(xx) "LDLR" (SEQ ID No:20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LDLR" encoded by a nucleic acid that hybridizes to the "LDLR" nucleic acid or its complement under low stringency conditions,

(xxi) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions,

(xxii) "NEDD5" (SEQ ID No:22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD5" encoded by a nucleic acid that hybridizes to the "NEDD5" nucleic acid or its complement under low stringency conditions,

(xxiii) "PLK" (SEQ ID No:23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLK" encoded by a nucleic acid that hybridizes to the "PLK" nucleic acid or its complement under low stringency conditions,

(xxiv) "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" (SEQ ID No:24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Proto-oncogene tyrosine kinase FYN (P59-

FYN, SYN, SLK) isoform 1" encoded by a nucleic acid that hybridizes to the "Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1" nucleic acid or its complement under low stringency conditions,

(xxv) "QPRT" (SEQ ID No:25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "QPRT" encoded by a nucleic acid that hybridizes to the "QPRT" nucleic acid or its complement under low stringency conditions,

(xxvi) "S-100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S-100 beta" encoded by a nucleic acid that hybridizes to the "S-100 beta" nucleic acid or its complement under low stringency conditions,

(xxvii) "SIM TO PLEXIN 1 - MOUSE" (SEQ ID No:27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO PLEXIN 1 - MOUSE" encoded by a nucleic acid that hybridizes to the "SIM TO PLEXIN 1 - MOUSE" nucleic acid or its complement under low stringency conditions,

(xxviii) "TGM5" (SEQ ID No:28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TGM5" encoded by a nucleic acid that hybridizes to the "TGM5" nucleic acid or its complement under low stringency conditions,

(xxix) "VLDL receptor" (SEQ ID No:29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLDL receptor" encoded by a nucleic acid that hybridizes to the "VLDL receptor" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "hypothetical protein FLJ11151" (SEQ ID No:30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein FLJ11151" encoded by a nucleic acid that hybridizes to the "hypothetical protein FLJ11151" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

The invention further relates to the following embodiments of the JIP1-complex

1. A protein complex selected from complex (I) and comprising

- (a) at least one first protein selected from the group consisting of:
- (i) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (ii) "ISLET-BRAIN 2" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISLET-BRAIN 2" encoded by a nucleic acid that hybridizes to the "ISLET-BRAIN 2" nucleic acid or its complement under low stringency conditions,
  - (iii) "JIP-1" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP-1" encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and
  - (iv) "JNK" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JNK" encoded by a nucleic acid that hybridizes to the "JNK" nucleic acid or its complement under low stringency conditions, and
- (b) at least one second protein, which second protein is selected from the group consisting of:
- (i) "ALPHA-CENTRACTIN" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-CENTRACTIN" encoded by a nucleic acid that hybridizes to the "ALPHA-CENTRACTIN" nucleic acid or its complement under low stringency conditions,
  - (ii) "CASPASE-14 PRECURSOR" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CASPASE-14 PRECURSOR" encoded by a nucleic acid that hybridizes to the "CASPASE-14 PRECURSOR" nucleic acid or its complement under low stringency conditions,
  - (iii) "DCTN1" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DCTN1" encoded by a nucleic acid that hybridizes to the "DCTN1" nucleic acid or its complement under low stringency conditions,
  - (iv) "Dynactin 3, isoform 2" (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Dynactin 3,

isoform 2" encoded by a nucleic acid that hybridizes to the "Dynactin 3, isoform 2" nucleic acid or its complement under low stringency conditions,

(v) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions,

(vi) "KINESIN HC" (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN HC" encoded by a nucleic acid that hybridizes to the "KINESIN HC" nucleic acid or its complement under low stringency conditions,

(vii) "KINESIN LC1" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN LC1" encoded by a nucleic acid that hybridizes to the "KINESIN LC1" nucleic acid or its complement under low stringency conditions,

(viii) "Kif5c" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Kif5c" encoded by a nucleic acid that hybridizes to the "Kif5c" nucleic acid or its complement under low stringency conditions, and

(ix) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Jip1 (SEQ ID NO. 37), or a functionally active derivative thereof, or a functionally active

fragment thereof, or a homolog thereof, or a variant of 'Jip1' encoded by a nucleic acid that hybridizes to the 'Jip1' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "ALPHA-CENTRACTIN" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-CENTRACTIN" encoded by a nucleic acid that hybridizes to the "ALPHA-CENTRACTIN" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "CASPASE-14 PRECURSOR" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CASPASE-14 PRECURSOR" encoded by a nucleic acid that hybridizes to the "CASPASE-14 PRECURSOR" nucleic acid or its complement under low stringency conditions,
- (iv) "DCTN1" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DCTN1" encoded by a nucleic acid that hybridizes to the "DCTN1" nucleic acid or its complement under low stringency conditions,
- (v) "Dynactin 3, isoform 2" (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Dynactin 3, isoform 2" encoded by a nucleic acid that hybridizes to the "Dynactin 3, isoform 2" nucleic acid or its complement under low stringency conditions,
- (vi) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions,
- (vii) "ISLET-BRAIN 2" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISLET-BRAIN



2" encoded by a nucleic acid that hybridizes to the "ISLET-BRAIN 2" nucleic acid or its complement under low stringency conditions,

(viii) "JIP-1" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP-1" encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,

(ix) "JNK" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JNK" encoded by a nucleic acid that hybridizes to the "JNK" nucleic acid or its complement under low stringency conditions,

(x) "KINESIN HC" (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN HC" encoded by a nucleic acid that hybridizes to the "KINESIN HC" nucleic acid or its complement under low stringency conditions,

(xi) "KINESIN LC1" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN LC1" encoded by a nucleic acid that hybridizes to the "KINESIN LC1" nucleic acid or its complement under low stringency conditions,

(xii) "Kif5c" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Kif5c" encoded by a nucleic acid that hybridizes to the "Kif5c" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions,

and a protein complex selected from complex (II) and comprising the following proteins:

(i) "ALPHA-CENTRACTIN" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-CENTRACTIN" encoded by a nucleic acid that hybridizes to the "ALPHA-CENTRACTIN" nucleic acid or its complement under low stringency conditions,

(ii) "CASPASE-14 PRECURSOR" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CASPASE-14 PRECURSOR" encoded by a nucleic acid that hybridizes to the

"CASPASE-14 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(iii) "DCTN1" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DCTN1" encoded by a nucleic acid that hybridizes to the "DCTN1" nucleic acid or its complement under low stringency conditions,

(iv) "Dynactin 3, isoform 2" (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Dynactin 3, isoform 2" encoded by a nucleic acid that hybridizes to the "Dynactin 3, isoform 2" nucleic acid or its complement under low stringency conditions,

(v) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions,

(vi) "ISLET-BRAIN 2" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISLET-BRAIN 2" encoded by a nucleic acid that hybridizes to the "ISLET-BRAIN 2" nucleic acid or its complement under low stringency conditions,

(vii) "JIP-1" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP-1" encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,

(viii) "KINESIN HC" (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN HC" encoded by a nucleic acid that hybridizes to the "KINESIN HC" nucleic acid or its complement under low stringency conditions,

(ix) "KINESIN LC1" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN LC1" encoded by a nucleic acid that hybridizes to the "KINESIN LC1" nucleic acid or its complement under low stringency conditions,

(x) "Kif5c" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Kif5c" encoded by a

nucleic acid that hybridizes to the "Kif5c" nucleic acid or its complement under low stringency conditions, and/or

(xi) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 8 of the following proteins:

(i) "ALPHA-CENTRACTIN" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-CENTRACTIN" encoded by a nucleic acid that hybridizes to the "ALPHA-CENTRACTIN" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "CASPASE-14 PRECURSOR" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CASPASE-14 PRECURSOR" encoded by a nucleic acid that hybridizes to the "CASPASE-14 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(iv) "DCTN1" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DCTN1" encoded by a nucleic acid that hybridizes to the "DCTN1" nucleic acid or its complement under low stringency conditions,

(v) "Dynactin 3, isoform 2" (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Dynactin 3, isoform 2" encoded by a nucleic acid that hybridizes to the "Dynactin 3, isoform 2" nucleic acid or its complement under low stringency conditions,

(vi) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11,

UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions,

(vii) "ISLET-BRAIN 2" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISLET-BRAIN 2" encoded by a nucleic acid that hybridizes to the "ISLET-BRAIN 2" nucleic acid or its complement under low stringency conditions,

(viii) "JIP-1" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP-1" encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,

(ix) "JNK" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JNK" encoded by a nucleic acid that hybridizes to the "JNK" nucleic acid or its complement under low stringency conditions,

(x) "KINESIN HC" (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN HC" encoded by a nucleic acid that hybridizes to the "KINESIN HC" nucleic acid or its complement under low stringency conditions,

(xi) "KINESIN LC1" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN LC1" encoded by a nucleic acid that hybridizes to the "KINESIN LC1" nucleic acid or its complement under low stringency conditions,

(xii) "Kif5c" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Kif5c" encoded by a nucleic acid that hybridizes to the "Kif5c" nucleic acid or its complement under low stringency conditions,

(xiii) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the

functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the JIP1 complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the JIP1 complex selected from

(i) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders;

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease and related disorders;

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing JIP1 complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the



presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "ALPHA-CENTRACTIN" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-CENTRACTIN" encoded by a nucleic acid that hybridizes to the "ALPHA-CENTRACTIN" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "CASPASE-14 PRECURSOR" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CASPASE-14 PRECURSOR" encoded by a nucleic acid that hybridizes to the

"CASPASE-14 PRECURSOR" nucleic acid or its complement under low stringency conditions, and/or

(iv) "DCTN1" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DCTN1" encoded by a nucleic acid that hybridizes to the "DCTN1" nucleic acid or its complement under low stringency conditions, and/or

(v) "Dynactin 3, isoform 2" (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Dynactin 3, isoform 2" encoded by a nucleic acid that hybridizes to the "Dynactin 3, isoform 2" nucleic acid or its complement under low stringency conditions, and/or

(vi) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(vii) "ISLET-BRAIN 2" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISLET-BRAIN 2" encoded by a nucleic acid that hybridizes to the "ISLET-BRAIN 2" nucleic acid or its complement under low stringency conditions, and/or

(viii) "JIP-1" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP-1" encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and/or

(ix) "JNK" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JNK" encoded by a nucleic acid that hybridizes to the "JNK" nucleic acid or its complement under low stringency conditions, and/or

(x) "KINESIN HC" (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN HC" encoded by a nucleic acid that hybridizes to the "KINESIN HC" nucleic acid or its complement under low stringency conditions, and/or

(xi) "KINESIN LC1" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN LC1"

encoded by a nucleic acid that hybridizes to the "KINESIN LC1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Kif5c" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Kif5c" encoded by a nucleic acid that hybridizes to the "Kif5c" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders;.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders;.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a

comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether  
(i) "ALPHA-CENTRACTIN" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-CENTRACTIN" encoded by a nucleic acid that hybridizes to the "ALPHA-CENTRACTIN" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or  
(iii) "CASPASE-14 PRECURSOR" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CASPASE-14 PRECURSOR" encoded by a nucleic acid that hybridizes to the "CASPASE-14 PRECURSOR" nucleic acid or its complement under low stringency conditions, and/or

- (iv) "DCTN1" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DCTN1" encoded by a nucleic acid that hybridizes to the "DCTN1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Dynactin 3, isoform 2" (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Dynactin 3, isoform 2" encoded by a nucleic acid that hybridizes to the "Dynactin 3, isoform 2" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "ISLET-BRAIN 2" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISLET-BRAIN 2" encoded by a nucleic acid that hybridizes to the "ISLET-BRAIN 2" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "JIP-1" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP-1" encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "JNK" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JNK" encoded by a nucleic acid that hybridizes to the "JNK" nucleic acid or its complement under low stringency conditions, and/or
- (x) "KINESIN HC" (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN HC" encoded by a nucleic acid that hybridizes to the "KINESIN HC" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "KINESIN LC1" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN LC1" encoded by a nucleic acid that hybridizes to the "KINESIN LC1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Kif5c" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Kif5c" encoded by a nucleic acid that hybridizes to the "Kif5c" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders;.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42 , wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "ALPHA-CENTRACTIN" (SEQ ID No:31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-CENTRACTIN" encoded by a nucleic acid that hybridizes to the "ALPHA-CENTRACTIN" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "CASPASE-14 PRECURSOR" (SEQ ID No:32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CASPASE-14 PRECURSOR" encoded by a nucleic acid that hybridizes to the "CASPASE-14 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(iv) "DCTN1" (SEQ ID No:33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DCTN1" encoded by a nucleic acid that hybridizes to the "DCTN1" nucleic acid or its complement under low stringency conditions,

(v) "Dynactin 3, isoform 2" (SEQ ID No:34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Dynactin 3, isoform 2" encoded by a nucleic acid that hybridizes to the "Dynactin 3, isoform 2" nucleic acid or its complement under low stringency conditions,

(vi) "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" (SEQ ID No:35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" encoded by a nucleic acid that hybridizes to the "HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN" nucleic acid or its complement under low stringency conditions,

(vii) "ISLET-BRAIN 2" (SEQ ID No:36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ISLET-BRAIN

2" encoded by a nucleic acid that hybridizes to the "ISLET-BRAIN 2" nucleic acid or its complement under low stringency conditions,

(viii) "JIP-1" (SEQ ID No:37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP-1" encoded by a nucleic acid that hybridizes to the "JIP-1" nucleic acid or its complement under low stringency conditions,

(ix) "JNK" (SEQ ID No:38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JNK" encoded by a nucleic acid that hybridizes to the "JNK" nucleic acid or its complement under low stringency conditions,

(x) "KINESIN HC" (SEQ ID No:39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN HC" encoded by a nucleic acid that hybridizes to the "KINESIN HC" nucleic acid or its complement under low stringency conditions,

(xi) "KINESIN LC1" (SEQ ID No:40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KINESIN LC1" encoded by a nucleic acid that hybridizes to the "KINESIN LC1" nucleic acid or its complement under low stringency conditions,

(xii) "Kif5c" (SEQ ID No:41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Kif5c" encoded by a nucleic acid that hybridizes to the "Kif5c" nucleic acid or its complement under low stringency conditions, and/or(xiii) "MAPK8IP3/JIP3" (SEQ ID No:21) or a functionally

active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAPK8IP3/JIP3" encoded by a nucleic acid that hybridizes to the "MAPK8IP3/JIP3" nucleic acid or its complement under low stringency conditions,as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders;.

The invention further relates to the following embodiments of the Fe65L2-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:



- (i) "APLP1" (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
  - (ii) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
  - (iii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and
  - (iv) "Fe65L2" (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions, and
- (b) at least one second protein, which second protein is selected from the group consisting of:
- (i) "CDC42BPB" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CDC42BPB" encoded by a nucleic acid that hybridizes to the "CDC42BPB" nucleic acid or its complement under low stringency conditions,
  - (ii) "COP9" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9" encoded by a nucleic acid that hybridizes to the "COP9" nucleic acid or its complement under low stringency conditions,
  - (iii) "COP9 COMPLEX SUBUNIT 4" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 COMPLEX SUBUNIT 4" encoded by a nucleic acid that hybridizes to the "COP9 COMPLEX SUBUNIT 4" nucleic acid or its complement under low stringency conditions,
  - (iv) "COP9 complex subunit 7a" (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 complex subunit 7a" encoded by a nucleic acid that hybridizes to the "COP9 complex subunit 7a" nucleic acid or its complement under low stringency conditions,

- (v) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (vi) "COPS5" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,
- (vii) "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" encoded by a nucleic acid that hybridizes to the "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS7B" (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7B" encoded by a nucleic acid that hybridizes to the "COPS7B" nucleic acid or its complement under low stringency conditions,
- (ix) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions,
- (x) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (xi) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions,
- (xii) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

- (xiii) "GPS1" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPS1" encoded by a nucleic acid that hybridizes to the "GPS1" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xv) "NEDD8" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD8" encoded by a nucleic acid that hybridizes to the "NEDD8" nucleic acid or its complement under low stringency conditions,
- (xvi) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,
- (xvii) "RBX1" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,
- (xviii) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,
- (xix) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,
- (xx) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions,

(xxi) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions,

(xxii) "TRIP15" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRIP15" encoded by a nucleic acid that hybridizes to the "TRIP15" nucleic acid or its complement under low stringency conditions,

(xxiii) "TUBGCP3" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TUBGCP3" encoded by a nucleic acid that hybridizes to the "TUBGCP3" nucleic acid or its complement under low stringency conditions, and

(xxiv) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Fe65L2 (SEQ ID NO. 53), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Fe65L2' encoded by a nucleic acid that hybridizes to the 'Fe65L2' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

(i) "APLP1" (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a

nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "CDC42BPB" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CDC42BPB" encoded by a nucleic acid that hybridizes to the "CDC42BPB" nucleic acid or its complement under low stringency conditions,

(v) "COP9" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9" encoded by a nucleic acid that hybridizes to the "COP9" nucleic acid or its complement under low stringency conditions,

(vi) "COP9 COMPLEX SUBUNIT 4" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 COMPLEX SUBUNIT 4" encoded by a nucleic acid that hybridizes to the "COP9 COMPLEX SUBUNIT 4" nucleic acid or its complement under low stringency conditions,

(vii) "COP9 complex subunit 7a" (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 complex subunit 7a" encoded by a nucleic acid that hybridizes to the "COP9 complex subunit 7a" nucleic acid or its complement under low stringency conditions,

(viii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(ix) "COPS5" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,

- (x) "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" encoded by a nucleic acid that hybridizes to the "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" nucleic acid or its complement under low stringency conditions,
- (xi) "COPS7B" (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7B" encoded by a nucleic acid that hybridizes to the "COPS7B" nucleic acid or its complement under low stringency conditions,
- (xii) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions,
- (xiii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (xiv) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions,
- (xv) "Fe65L2" (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
- (xvi) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xvii) "GPS1" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPS1" encoded by a nucleic acid that hybridizes to the "GPS1" nucleic acid or its complement under low stringency conditions,

- (xviii) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xix) "NEDD8" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD8" encoded by a nucleic acid that hybridizes to the "NEDD8" nucleic acid or its complement under low stringency conditions,
- (xx) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,
- (xxi) "RBX1" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,
- (xxii) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,
- (xxiii) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,
- (xxiv) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions,
- (xxv) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes

to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions,

(xxvi) "TRIP15" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRIP15" encoded by a nucleic acid that hybridizes to the "TRIP15" nucleic acid or its complement under low stringency conditions,

(xxvii) "TUBGCP3" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TUBGCP3" encoded by a nucleic acid that hybridizes to the "TUBGCP3" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 23 of the following proteins:

(i) "APLP1" (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "CDC42BPB" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CDC42BPB" encoded by a nucleic acid that hybridizes to the "CDC42BPB" nucleic acid or its complement under low stringency conditions,



- (v) "COP9" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9" encoded by a nucleic acid that hybridizes to the "COP9" nucleic acid or its complement under low stringency conditions,
- (vi) "COP9 COMPLEX SUBUNIT 4" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 COMPLEX SUBUNIT 4" encoded by a nucleic acid that hybridizes to the "COP9 COMPLEX SUBUNIT 4" nucleic acid or its complement under low stringency conditions,
- (vii) "COP9 complex subunit 7a" (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 complex subunit 7a" encoded by a nucleic acid that hybridizes to the "COP9 complex subunit 7a" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (ix) "COPS5" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,
- (x) "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" encoded by a nucleic acid that hybridizes to the "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" nucleic acid or its complement under low stringency conditions,
- (xi) "COPS7B" (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7B" encoded by a nucleic acid that hybridizes to the "COPS7B" nucleic acid or its complement under low stringency conditions,
- (xii) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions,

- (xiii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (xiv) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions,
- (xv) "Fe65L2" (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
- (xvi) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xvii) "GPS1" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPS1" encoded by a nucleic acid that hybridizes to the "GPS1" nucleic acid or its complement under low stringency conditions,
- (xviii) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xix) "NEDD8" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD8" encoded by a nucleic acid that hybridizes to the "NEDD8" nucleic acid or its complement under low stringency conditions,
- (xx) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,

(xxi) "RBX1" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,

(xxii) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

(xxiii) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(xxiv) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions,

(xxv) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions,

(xxvi) "TRIP15" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRIP15" encoded by a nucleic acid that hybridizes to the "TRIP15" nucleic acid or its complement under low stringency conditions,

(xxvii) "TUBGCP3" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TUBGCP3" encoded by a nucleic acid that hybridizes to the "TUBGCP3" nucleic acid or its complement under low stringency conditions,

(xxviii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65L2 obtainable by a process according to any of No. 9 - 11.
13. Protein of the Fe65L2 selected from
  - (i) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions,
  - (ii) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
  - (iii) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
  - (iv) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,
  - (v) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,
  - (vi) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2"

encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(vii) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions,

(viii) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions, and

(ix) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.
18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
19. The kit according to No. 18 for processing a substrate of said complex.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; cancer such as prostate cancer and breast cancer and skin cancer .
21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.
22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions,

(ii) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(iii) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(iv) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,

(v) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

(vi) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(vii) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions,

(viii) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a



variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(ix) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease; cancer such as prostate cancer and breast cancer and skin cancer .

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions,

(ii) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(iii) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(iv) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,

- (v) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,
- (vi) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,
- (vii) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions,
- (viii) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, comprising the steps of
  - (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing Fe65L2 to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether  
(i) "APLP1" (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

- (iv) "CDC42BPB" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CDC42BPB" encoded by a nucleic acid that hybridizes to the "CDC42BPB" nucleic acid or its complement under low stringency conditions, and/or
- (v) "COP9" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9" encoded by a nucleic acid that hybridizes to the "COP9" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "COP9 COMPLEX SUBUNIT 4" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 COMPLEX SUBUNIT 4" encoded by a nucleic acid that hybridizes to the "COP9 COMPLEX SUBUNIT 4" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "COP9 complex subunit 7a" (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 complex subunit 7a" encoded by a nucleic acid that hybridizes to the "COP9 complex subunit 7a" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "COPS5" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions, and/or
- (x) "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" encoded by a nucleic acid that hybridizes to the "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "COPS7B" (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7B" encoded by a

nucleic acid that hybridizes to the "COPS7B" nucleic acid or its complement under low stringency conditions, and/or

(xii) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Fe65L2" (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "GPS1" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPS1" encoded by a nucleic acid that hybridizes to the "GPS1" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xix) "NEDD8" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD8" encoded by a

nucleic acid that hybridizes to the "NEDD8" nucleic acid or its complement under low stringency conditions, and/or

(xx) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "RBX1" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "TRIP15" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRIP15" encoded by a nucleic acid that hybridizes to the "TRIP15" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "TUBGCP3" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TUBGCP3"

encoded by a nucleic acid that hybridizes to the "TUBGCP3" nucleic acid or its complement under low stringency conditions, and/or (xxviii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; cancer such as prostate cancer and breast cancer and skin cancer .

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; cancer such as prostate cancer and breast cancer and skin cancer .

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not

having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "APLP1" (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CDC42BPB" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CDC42BPB" encoded by a nucleic acid that hybridizes to the "CDC42BPB" nucleic acid or its complement under low stringency conditions, and/or



- (v) "COP9" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9" encoded by a nucleic acid that hybridizes to the "COP9" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "COP9 COMPLEX SUBUNIT 4" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 COMPLEX SUBUNIT 4" encoded by a nucleic acid that hybridizes to the "COP9 COMPLEX SUBUNIT 4" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "COP9 complex subunit 7a" (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 complex subunit 7a" encoded by a nucleic acid that hybridizes to the "COP9 complex subunit 7a" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "COPS5" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions, and/or
- (x) "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" encoded by a nucleic acid that hybridizes to the "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "COPS7B" (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7B" encoded by a nucleic acid that hybridizes to the "COPS7B" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a

nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Fe65L2" (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "GPS1" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPS1" encoded by a nucleic acid that hybridizes to the "GPS1" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xix) "NEDD8" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD8" encoded by a nucleic acid that hybridizes to the "NEDD8" nucleic acid or its complement under low stringency conditions, and/or

(xx) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the

"Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "RBX1" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "TRIP15" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRIP15" encoded by a nucleic acid that hybridizes to the "TRIP15" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "TUBGCP3" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TUBGCP3" encoded by a nucleic acid that hybridizes to the "TUBGCP3" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11"

encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; cancer such as prostate cancer and breast cancer and skin cancer .

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42 , wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "APLP1" (SEQ ID No:42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "CDC42BPB" (SEQ ID No:43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CDC42BPB" encoded by a nucleic acid that hybridizes to the "CDC42BPB" nucleic acid or its complement under low stringency conditions,
- (v) "COP9" (SEQ ID No:44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9" encoded by a nucleic acid that hybridizes to the "COP9" nucleic acid or its complement under low stringency conditions,
- (vi) "COP9 COMPLEX SUBUNIT 4" (SEQ ID No:45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 COMPLEX SUBUNIT 4" encoded by a nucleic acid that hybridizes to the "COP9 COMPLEX SUBUNIT 4" nucleic acid or its complement under low stringency conditions,
- (vii) "COP9 complex subunit 7a" (SEQ ID No:46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COP9 complex subunit 7a" encoded by a nucleic acid that hybridizes to the "COP9 complex subunit 7a" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (ix) "COPS5" (SEQ ID No:48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a

nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,

(x) "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" (SEQ ID No:49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" encoded by a nucleic acid that hybridizes to the "COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)" nucleic acid or its complement under low stringency conditions,

(xi) "COPS7B" (SEQ ID No:50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7B" encoded by a nucleic acid that hybridizes to the "COPS7B" nucleic acid or its complement under low stringency conditions,

(xii) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions,

(xiii) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,

(xiv) "FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ12599" encoded by a nucleic acid that hybridizes to the "FLJ12599" nucleic acid or its complement under low stringency conditions,

(xv) "Fe65L2" (SEQ ID No:53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,

(xvi) "GPR49" (SEQ ID No:54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(xvii) "GPS1" (SEQ ID No:55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPS1" encoded by a

nucleic acid that hybridizes to the "GPS1" nucleic acid or its complement under low stringency conditions,

(xviii) "KIAA1102 PROTEIN (FRAGMENT)" (SEQ ID No:56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1102 PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xix) "NEDD8" (SEQ ID No:57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEDD8" encoded by a nucleic acid that hybridizes to the "NEDD8" nucleic acid or its complement under low stringency conditions,

(xx) "Protocadherin gamma C3" (SEQ ID No:58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin gamma C3" encoded by a nucleic acid that hybridizes to the "Protocadherin gamma C3" nucleic acid or its complement under low stringency conditions,

(xxi) "RBX1" (SEQ ID No:59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,

(xxii) "RHOBTB1" (SEQ ID No:60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

(xxiii) "RHOBTB2" (SEQ ID No:61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(xxiv) "SIM TO CGI-20" (SEQ ID No:62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO CGI-20" encoded by a nucleic acid that hybridizes to the "SIM TO CGI-20" nucleic acid or its complement under low stringency conditions,

(xxv) "SIMILAR TO POL POLYPROTEIN" (SEQ ID No:63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a

variant of "SIMILAR TO POL POLYPROTEIN" encoded by a nucleic acid that hybridizes to the "SIMILAR TO POL POLYPROTEIN" nucleic acid or its complement under low stringency conditions,

(xxvi) "TRIP15" (SEQ ID No:64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRIP15" encoded by a nucleic acid that hybridizes to the "TRIP15" nucleic acid or its complement under low stringency conditions,

(xxvii) "TUBGCP3" (SEQ ID No:65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TUBGCP3" encoded by a nucleic acid that hybridizes to the "TUBGCP3" nucleic acid or its complement under low stringency conditions, and/or (xxviii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; cancer such as prostate cancer and breast cancer and skin cancer .

The invention further relates to the following embodiments of the Pilt-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "DLG1" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLG1" encoded by a nucleic acid that hybridizes to the "DLG1" nucleic acid or its complement under low stringency conditions, and

(ii) "Pilt" (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Pilt" encoded by a nucleic acid that hybridizes to the "Pilt" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a



variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(ii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions,

(iii) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,

(iv) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions,

(v) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(vi) "STMN3" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STMN3" encoded by a nucleic acid that hybridizes to the "STMN3" nucleic acid or its complement under low stringency conditions, and

(vii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a

buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Pilt (SEQ ID NO. 72), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Pilt' encoded by a nucleic acid that hybridizes to the 'Pilt' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "DLG1" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLG1" encoded by a nucleic acid that hybridizes to the "DLG1" nucleic acid or its complement under low stringency conditions,
- (ii) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (iii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions,
- (iv) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,
- (v) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions,

- (vi) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (vii) "Pilt" (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Pilt" encoded by a nucleic acid that hybridizes to the "Pilt" nucleic acid or its complement under low stringency conditions,
- (viii) "STMN3" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STMN3" encoded by a nucleic acid that hybridizes to the "STMN3" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 6 of the following proteins:

- (i) "DLG1" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLG1" encoded by a nucleic acid that hybridizes to the "DLG1" nucleic acid or its complement under low stringency conditions,
- (ii) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (iii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions,

- (iv) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,
- (v) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions,
- (vi) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (vii) "Pilt" (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Pilt" encoded by a nucleic acid that hybridizes to the "Pilt" nucleic acid or its complement under low stringency conditions,
- (viii) "STMN3" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STMN3" encoded by a nucleic acid that hybridizes to the "STMN3" nucleic acid or its complement under low stringency conditions,
- (ix) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Pilt obtainable by a process according to any of No. 9 - 11.

13. Protein of the Pilt selected from

- (i) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (ii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions,
- (iii) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,
- (iv) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions, and
- (v) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.
18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
19. The kit according to No. 18 for processing a substrate of said complex.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as

Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and atherosclerosis.

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(ii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions,

(iii) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,

(iv) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions, and/or

(v) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949



(FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and atherosclerosis.

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (ii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions,
- (iii) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,
- (iv) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions, and/or
- (v) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949

(FRAGMENT)" nucleic acid or its complement under low stringency conditions, comprising the steps of

- (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing it to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "DLG1" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLG1" encoded by a nucleic acid that hybridizes to the "DLG1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(iii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions, and/or

(iv) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions, and/or

(v) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions, and/or

(vi) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Pilt" (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Pilt" encoded by a nucleic

acid that hybridizes to the "Pilt" nucleic acid or its complement under low stringency conditions, and/or

(viii) "STMN3" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STMN3" encoded by a nucleic acid that hybridizes to the "STMN3" nucleic acid or its complement under low stringency conditions, and/or

(ix) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and arteriosclerosis.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and arteriosclerosis.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent

on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "DLG1" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLG1" encoded by a nucleic acid that hybridizes to the "DLG1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(iii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that

hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions, and/or

(iv) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions, and/or

(v) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions, and/or

(vi) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Pilt" (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Pilt" encoded by a nucleic acid that hybridizes to the "Pilt" nucleic acid or its complement under low stringency conditions, and/or

(viii) "STMN3" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STMN3" encoded by a nucleic acid that hybridizes to the "STMN3" nucleic acid or its complement under low stringency conditions, and/or

(ix) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and arteriosclerosis.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "DLG1" (SEQ ID No:67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLG1" encoded by a nucleic acid that hybridizes to the "DLG1" nucleic acid or its complement under low stringency conditions,  
(ii) "HYPOTHETICAL PROTEIN (FRAGMENT)" (SEQ ID No:68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

- (iii) "HYPOTHETICAL PROTEIN FLJ12599" (SEQ ID No:52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ12599" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ12599" nucleic acid or its complement under low stringency conditions,
- (iv) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,
- (v) "KIAA1102 (Fragment) " (SEQ ID No:70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102 (Fragment) " encoded by a nucleic acid that hybridizes to the "KIAA1102 (Fragment) " nucleic acid or its complement under low stringency conditions,
- (vi) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (vii) "Pilt" (SEQ ID No:72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Pilt" encoded by a nucleic acid that hybridizes to the "Pilt" nucleic acid or its complement under low stringency conditions,
- (viii) "STMN3" (SEQ ID No:73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STMN3" encoded by a nucleic acid that hybridizes to the "STMN3" nucleic acid or its complement under low stringency conditions, and/or (ix) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and atherosclerosis.



The invention further relates to the following embodiments of the Neurotrypsin-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "ADAMTS1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS1" encoded by a nucleic acid that hybridizes to the "ADAMTS1" nucleic acid or its complement under low stringency conditions,

(ii) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions,

(iii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions,

(iv) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,

(v) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions,

(vi) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions,

- (vii) "DECR1" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DECR1" encoded by a nucleic acid that hybridizes to the "DECR1" nucleic acid or its complement under low stringency conditions,
- (viii) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,
- (ix) "ERP70" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ERP70" encoded by a nucleic acid that hybridizes to the "ERP70" nucleic acid or its complement under low stringency conditions,
- (x) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions,
- (xi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions,
- (xii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xiii) "LAMB1" (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAMB1" encoded by a nucleic acid that hybridizes to the "LAMB1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

- (xv) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions,
- (xvi) "NOTCH4-like protein (Hypothetical protein)" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NOTCH4-like protein (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "NOTCH4-like protein (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,
- (xvii) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16" encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions,
- (xviii) "PLOD" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD" encoded by a nucleic acid that hybridizes to the "PLOD" nucleic acid or its complement under low stringency conditions,
- (xix) "PLOD3" (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD3" encoded by a nucleic acid that hybridizes to the "PLOD3" nucleic acid or its complement under low stringency conditions,
- (xx) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions,
- (xxi) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions,
- (xxii) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a

nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xxiii) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions,

(xxiv) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions,

(xxv) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11" encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions,

(xxvi) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions,

(xxvii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions,

(xxviii) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, and

(xxix) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said

second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Neurotrypsin (SEQ ID NO. 91), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Neurotrypsin' encoded by a nucleic acid that hybridizes to the 'Neurotrypsin' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "ADAMTS1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS1" encoded by a nucleic acid that hybridizes to the "ADAMTS1" nucleic acid or its complement under low stringency conditions,
- (ii) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions,
- (iii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions,
- (iv) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,
- (v) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a

nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions,

(vi) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions,

(vii) "DECR1" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DECR1" encoded by a nucleic acid that hybridizes to the "DECR1" nucleic acid or its complement under low stringency conditions,

(viii) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,

(ix) "ERP70" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ERP70" encoded by a nucleic acid that hybridizes to the "ERP70" nucleic acid or its complement under low stringency conditions,

(x) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions,

(xi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions,

(xii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xiii) "LAMB1" (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAMB1" encoded by a

nucleic acid that hybridizes to the "LAMB1" nucleic acid or its complement under low stringency conditions,

(xiv) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xv) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions,

(xvi) "NOTCH4-like protein (Hypothetical protein)" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NOTCH4-like protein (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "NOTCH4-like protein (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,

(xvii) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xviii) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16" encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions,

(xix) "PLOD" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD" encoded by a nucleic acid that hybridizes to the "PLOD" nucleic acid or its complement under low stringency conditions,

(xx) "PLOD3" (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD3" encoded by a nucleic acid that hybridizes to the "PLOD3" nucleic acid or its complement under low stringency conditions,

(xxi) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38

SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions,

(xxii) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions,

(xxiii) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xxiv) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions,

(xxv) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions,

(xxvi) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11" encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions,

(xxvii) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions,

(xxviii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2"



encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions,

(xxix) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 28 of the following proteins:

(i) "ADAMTS1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS1" encoded by a nucleic acid that hybridizes to the "ADAMTS1" nucleic acid or its complement under low stringency conditions,

(ii) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions,

(iii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions,

(iv) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,

(v) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions,

- (vi) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions,
- (vii) "DECR1" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DECR1" encoded by a nucleic acid that hybridizes to the "DECR1" nucleic acid or its complement under low stringency conditions,
- (viii) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,
- (ix) "ERP70" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ERP70" encoded by a nucleic acid that hybridizes to the "ERP70" nucleic acid or its complement under low stringency conditions,
- (x) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions,
- (xi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions,
- (xii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xiii) "LAMB1" (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAMB1" encoded by a nucleic acid that hybridizes to the "LAMB1" nucleic acid or its complement under low stringency conditions,

(xiv) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xv) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions,

(xvi) "NOTCH4-like protein (Hypothetical protein)" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NOTCH4-like protein (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "NOTCH4-like protein (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,

(xvii) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xviii) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16" encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions,

(xix) "PLOD" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD" encoded by a nucleic acid that hybridizes to the "PLOD" nucleic acid or its complement under low stringency conditions,

(xx) "PLOD3" (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD3" encoded by a nucleic acid that hybridizes to the "PLOD3" nucleic acid or its complement under low stringency conditions,

(xxi) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA

POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions,

(xxii) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions,

(xxiii) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xxiv) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions,

(xxv) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions,

(xxvi) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11" encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions,

(xxvii) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions,

(xxviii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions,

(xxix) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, (xxx) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Neurotrypsin obtainable by a process according to any of No. 9 - 11.
13. Protein of the Neurotrypsin selected from
- (i) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions,
  - (ii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions,
  - (iii) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions,
  - (iv) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions,

- (v) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions,
- (vi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions,
- (vii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (viii) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions,
- (ix) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16" encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions,
- (x) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions,
- (xi) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions,
- (xii) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a

nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions,

(xiii) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions,

(xiv) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11" encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions,

(xv) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions, and

(xvi) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or



(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions,
- (ii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions,
- (iii) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions,
- (iv) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions,
- (v) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions,
- (vi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions,

(vii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions,

(viii) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions,

(ix) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16" encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions,

(x) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions,

(xi) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions,

(xii) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions,

(xiii) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions,

(xiv) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11" encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions,

(xv) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions,
- (ii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions,
- (iii) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a

nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions,

(iv) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions,

(v) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions,

(vi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions,

(vii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions,

(viii) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions,

(ix) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16" encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions,

(x) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions,

- (xi) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions,
- (xii) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions,
- (xiii) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions,
- (xiv) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11" encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions,
- (xv) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions, comprising the steps of
  - (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8

comprising the steps of (a) exposing said complex, or a cell or organism containing Neurotrypsin to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "ADAMTS1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS1" encoded by a nucleic acid that hybridizes to the "ADAMTS1" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "DECR1" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DECR1" encoded by a nucleic acid that hybridizes to the "DECR1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "ERP70" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ERP70" encoded by a nucleic acid that hybridizes to the "ERP70" nucleic acid or its complement under low stringency conditions, and/or
- (x) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a



nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions, and/or

(xi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "LAMB1" (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAMB1" encoded by a nucleic acid that hybridizes to the "LAMB1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions, and/or

(xv) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "NOTCH4-like protein (Hypothetical protein)" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NOTCH4-like protein (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "NOTCH4-like protein (Hypothetical protein)" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16"

encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions, and/or

(xix) "PLOD" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD" encoded by a nucleic acid that hybridizes to the "PLOD" nucleic acid or its complement under low stringency conditions, and/or

(xx) "PLOD3" (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD3" encoded by a nucleic acid that hybridizes to the "PLOD3" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11" encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether

- (i) "ADAMTS1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS1" encoded by a nucleic acid that hybridizes to the "ADAMTS1" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "DECR1" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DECR1" encoded by a nucleic acid that hybridizes to the "DECR1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "ERP70" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ERP70" encoded by a

nucleic acid that hybridizes to the "ERP70" nucleic acid or its complement under low stringency conditions, and/or

(x) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions, and/or

(xi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "LAMB1" (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAMB1" encoded by a nucleic acid that hybridizes to the "LAMB1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions, and/or

(xv) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "NOTCH4-like protein (Hypothetical protein)" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NOTCH4-like protein (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "NOTCH4-like protein (Hypothetical protein)" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin"

encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16" encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions, and/or

(xix) "PLOD" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD" encoded by a nucleic acid that hybridizes to the "PLOD" nucleic acid or its complement under low stringency conditions, and/or

(xx) "PLOD3" (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD3" encoded by a nucleic acid that hybridizes to the "PLOD3" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11" encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as



neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
 (i) "ADAMTS1" (SEQ ID No:75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS1" encoded by a nucleic acid that hybridizes to the "ADAMTS1" nucleic acid or its complement under low stringency conditions,  
 (ii) "ADAMTS19" (SEQ ID No:76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS19" encoded by a nucleic acid that hybridizes to the "ADAMTS19" nucleic acid or its complement under low stringency conditions,

- (iii) "ADAMTS7" (SEQ ID No:77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ADAMTS7" encoded by a nucleic acid that hybridizes to the "ADAMTS7" nucleic acid or its complement under low stringency conditions,
- (iv) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,
- (v) "CRTAP" (SEQ ID No:79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRTAP" encoded by a nucleic acid that hybridizes to the "CRTAP" nucleic acid or its complement under low stringency conditions,
- (vi) "CU70\_HUMAN" (SEQ ID No:80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CU70\_HUMAN" encoded by a nucleic acid that hybridizes to the "CU70\_HUMAN" nucleic acid or its complement under low stringency conditions,
- (vii) "DECR1" (SEQ ID No:81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DECR1" encoded by a nucleic acid that hybridizes to the "DECR1" nucleic acid or its complement under low stringency conditions,
- (viii) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,
- (ix) "ERP70" (SEQ ID No:83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ERP70" encoded by a nucleic acid that hybridizes to the "ERP70" nucleic acid or its complement under low stringency conditions,
- (x) "GBTS1" (SEQ ID No:84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GBTS1" encoded by a nucleic acid that hybridizes to the "GBTS1" nucleic acid or its complement under low stringency conditions,
- (xi) "GRCB" (SEQ ID No:85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GRCB" encoded by a

nucleic acid that hybridizes to the "GRCB" nucleic acid or its complement under low stringency conditions,

(xii) "Hypothetical protein KIAA1402 (Fragment)" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1402 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1402 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xiii) "LAMB1" (SEQ ID No:87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAMB1" encoded by a nucleic acid that hybridizes to the "LAMB1" nucleic acid or its complement under low stringency conditions,

(xiv) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xv) "MT-ACT48" (SEQ ID No:89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MT-ACT48" encoded by a nucleic acid that hybridizes to the "MT-ACT48" nucleic acid or its complement under low stringency conditions,

(xvi) "NOTCH4-like protein (Hypothetical protein)" (SEQ ID No:90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NOTCH4-like protein (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "NOTCH4-like protein (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,

(xvii) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xviii) "PCDH16" (SEQ ID No:92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PCDH16" encoded by a nucleic acid that hybridizes to the "PCDH16" nucleic acid or its complement under low stringency conditions,

(xix) "PLOD" (SEQ ID No:93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD" encoded by a

nucleic acid that hybridizes to the "PLOD" nucleic acid or its complement under low stringency conditions,

(xx) "PLOD3" (SEQ ID No:94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLOD3" encoded by a nucleic acid that hybridizes to the "PLOD3" nucleic acid or its complement under low stringency conditions,

(xxi) "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" encoded by a nucleic acid that hybridizes to the "PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT" nucleic acid or its complement under low stringency conditions,

(xxii) "RAB39, MEMBER RAS ONCOGENE FAMILY" (SEQ ID No:96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB39, MEMBER RAS ONCOGENE FAMILY" encoded by a nucleic acid that hybridizes to the "RAB39, MEMBER RAS ONCOGENE FAMILY" nucleic acid or its complement under low stringency conditions,

(xxiii) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xxiv) "SC65" (SEQ ID No:98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SC65" encoded by a nucleic acid that hybridizes to the "SC65" nucleic acid or its complement under low stringency conditions,

(xxv) "Similar to RIKEN cDNA 1300010F03 gene" (SEQ ID No:99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1300010F03 gene" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1300010F03 gene" nucleic acid or its complement under low stringency conditions,

(xxvi) "Similar to hydroxysteroid 17-beta dehydrogenase 11" (SEQ ID No:100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hydroxysteroid 17-beta dehydrogenase 11"

encoded by a nucleic acid that hybridizes to the "Similar to hydroxysteroid 17-beta dehydrogenase 11" nucleic acid or its complement under low stringency conditions, (xxvii) "Similar to hypothetical protein FLJ22329" (SEQ ID No:101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to hypothetical protein FLJ22329" encoded by a nucleic acid that hybridizes to the "Similar to hypothetical protein FLJ22329" nucleic acid or its complement under low stringency conditions, (xxviii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions, (xxix) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, and/or (xxx) "q8wvi0" (SEQ ID No:104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "q8wvi0" encoded by a nucleic acid that hybridizes to the "q8wvi0" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the following embodiments of the Hunc18a-complex

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Epim" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Epim" encoded by a nucleic acid that hybridizes to the "Epim" nucleic acid or its complement under low stringency conditions,
    - (ii) "Hunc18a" (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hunc18a"

encoded by a nucleic acid that hybridizes to the "Hunc18a" nucleic acid or its complement under low stringency conditions,

(iii) "STX1A" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1A" encoded by a nucleic acid that hybridizes to the "STX1A" nucleic acid or its complement under low stringency conditions,

(iv) "STX1B2" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1B2" encoded by a nucleic acid that hybridizes to the "STX1B2" nucleic acid or its complement under low stringency conditions,

(v) "STX3A" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX3A" encoded by a nucleic acid that hybridizes to the "STX3A" nucleic acid or its complement under low stringency conditions,

(vi) "X11alpha" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11alpha" encoded by a nucleic acid that hybridizes to the "X11alpha" nucleic acid or its complement under low stringency conditions, and

(vii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "ELAVL1" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ELAVL1" encoded by a nucleic acid that hybridizes to the "ELAVL1" nucleic acid or its complement under low stringency conditions,

(ii) "FIGF" (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FIGF" encoded by a nucleic acid that hybridizes to the "FIGF" nucleic acid or its complement under low stringency conditions,

(iii) "Filamin, gamma" (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Filamin,

gamma" encoded by a nucleic acid that hybridizes to the "Filamin, gamma" nucleic acid or its complement under low stringency conditions,

(iv) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions,

(v) "PAWR" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PAWR" encoded by a nucleic acid that hybridizes to the "PAWR" nucleic acid or its complement under low stringency conditions, and

(vi) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Hunc18a (SEQ ID NO. 110), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Hunc18a' encoded by a nucleic acid that hybridizes to the 'Hunc18a' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

(i) "ELAVL1" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ELAVL1" encoded by a nucleic acid that hybridizes to the "ELAVL1" nucleic acid or its complement under low stringency conditions,

- (ii) "Epim" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Epim" encoded by a nucleic acid that hybridizes to the "Epim" nucleic acid or its complement under low stringency conditions,
- (iii) "FIGF" (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FIGF" encoded by a nucleic acid that hybridizes to the "FIGF" nucleic acid or its complement under low stringency conditions,
- (iv) "Filamin, gamma" (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Filamin, gamma" encoded by a nucleic acid that hybridizes to the "Filamin, gamma" nucleic acid or its complement under low stringency conditions,
- (v) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions,
- (vi) "Hunc18a" (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hunc18a" encoded by a nucleic acid that hybridizes to the "Hunc18a" nucleic acid or its complement under low stringency conditions,
- (vii) "PAWR" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PAWR" encoded by a nucleic acid that hybridizes to the "PAWR" nucleic acid or its complement under low stringency conditions,
- (viii) "STX1A" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1A" encoded by a nucleic acid that hybridizes to the "STX1A" nucleic acid or its complement under low stringency conditions,
- (ix) "STX1B2" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1B2" encoded by a nucleic acid that hybridizes to the "STX1B2" nucleic acid or its complement under low stringency conditions,
- (x) "STX3A" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX3A" encoded by a



nucleic acid that hybridizes to the "STX3A" nucleic acid or its complement under low stringency conditions,

(xi) "X11alpha" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11alpha" encoded by a nucleic acid that hybridizes to the "X11alpha" nucleic acid or its complement under low stringency conditions,

(xii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions,

and a protein complex selected from complex (II) and comprising the following proteins:

(i) "ELAVL1" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ELAVL1" encoded by a nucleic acid that hybridizes to the "ELAVL1" nucleic acid or its complement under low stringency conditions,

(ii) "Epim" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Epim" encoded by a nucleic acid that hybridizes to the "Epim" nucleic acid or its complement under low stringency conditions,

(iii) "FIGF" (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FIGF" encoded by a nucleic acid that hybridizes to the "FIGF" nucleic acid or its complement under low stringency conditions,

(iv) "Filamin, gamma" (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Filamin, gamma" encoded by a nucleic acid that hybridizes to the "Filamin, gamma" nucleic acid or its complement under low stringency conditions,

(v) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3"

encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions,

(vi) "Hunc18a" (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hunc18a" encoded by a nucleic acid that hybridizes to the "Hunc18a" nucleic acid or its complement under low stringency conditions,

(vii) "PAWR" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PAWR" encoded by a nucleic acid that hybridizes to the "PAWR" nucleic acid or its complement under low stringency conditions,

(viii) "STX1A" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1A" encoded by a nucleic acid that hybridizes to the "STX1A" nucleic acid or its complement under low stringency conditions,

(ix) "STX1B2" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1B2" encoded by a nucleic acid that hybridizes to the "STX1B2" nucleic acid or its complement under low stringency conditions,

(x) "STX3A" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX3A" encoded by a nucleic acid that hybridizes to the "STX3A" nucleic acid or its complement under low stringency conditions, and/or

(xi) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 5 of the following proteins:

(i) "ELAVL1" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ELAVL1" encoded by a nucleic acid that hybridizes to the "ELAVL1" nucleic acid or its complement under low stringency conditions,

- (ii) "Epim" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Epim" encoded by a nucleic acid that hybridizes to the "Epim" nucleic acid or its complement under low stringency conditions,
- (iii) "FIGF" (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FIGF" encoded by a nucleic acid that hybridizes to the "FIGF" nucleic acid or its complement under low stringency conditions,
- (iv) "Filamin, gamma" (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Filamin, gamma" encoded by a nucleic acid that hybridizes to the "Filamin, gamma" nucleic acid or its complement under low stringency conditions,
- (v) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions,
- (vi) "Hunc18a" (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hunc18a" encoded by a nucleic acid that hybridizes to the "Hunc18a" nucleic acid or its complement under low stringency conditions,
- (vii) "PAWR" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PAWR" encoded by a nucleic acid that hybridizes to the "PAWR" nucleic acid or its complement under low stringency conditions,
- (viii) "STX1A" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1A" encoded by a nucleic acid that hybridizes to the "STX1A" nucleic acid or its complement under low stringency conditions,
- (ix) "STX1B2" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1B2" encoded by a nucleic acid that hybridizes to the "STX1B2" nucleic acid or its complement under low stringency conditions,
- (x) "STX3A" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX3A" encoded by a

nucleic acid that hybridizes to the "STX3A" nucleic acid or its complement under low stringency conditions,

(xi) "X11alpha" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11alpha" encoded by a nucleic acid that hybridizes to the "X11alpha" nucleic acid or its complement under low stringency conditions,

(xii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,

(xiii) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the

expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Hunc18a obtainable by a process according to any of No. 9 - 11.

13. Protein of the Hunc18a selected from

- (i) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions, and
- (ii) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer

comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
19. The kit according to No. 18 for processing a substrate of said complex.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders; .
21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.
22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.
24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease and related disorders; .

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions, and/or

(ii) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing Hunc18a to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.



27. The method of No. 26, wherein the amount of said complex is determined.
28. The method of No. 26, wherein the activity of said complex is determined.
29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.
31. The method of No. 30, wherein said determining step comprises determining whether
- (i) "ELAVL1" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ELAVL1" encoded by a nucleic acid that hybridizes to the "ELAVL1" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "Epim" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Epim" encoded by a nucleic acid that hybridizes to the "Epim" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "FIGF" (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FIGF" encoded by a nucleic acid that hybridizes to the "FIGF" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "Filamin, gamma" (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Filamin, gamma" encoded by a nucleic acid that hybridizes to the "Filamin, gamma" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions, and/or

- (vi) "Hunc18a" (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hunc18a" encoded by a nucleic acid that hybridizes to the "Hunc18a" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "PAWR" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PAWR" encoded by a nucleic acid that hybridizes to the "PAWR" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "STX1A" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1A" encoded by a nucleic acid that hybridizes to the "STX1A" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "STX1B2" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1B2" encoded by a nucleic acid that hybridizes to the "STX1B2" nucleic acid or its complement under low stringency conditions, and/or
- (x) "STX3A" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX3A" encoded by a nucleic acid that hybridizes to the "STX3A" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "X11alpha" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11alpha" encoded by a nucleic acid that hybridizes to the "X11alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders; .
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders; .
34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said

complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "ELAVL1" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ELAVL1" encoded by a nucleic acid that hybridizes to the "ELAVL1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Epim" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Epim" encoded by a nucleic acid that hybridizes to the "Epim" nucleic acid or its complement under low stringency conditions, and/or

(iii) "FIGF" (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FIGF" encoded by a nucleic acid that hybridizes to the "FIGF" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Filamin, gamma" (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Filamin, gamma" encoded by a nucleic acid that hybridizes to the "Filamin, gamma" nucleic acid or its complement under low stringency conditions, and/or

(v) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Hunc18a" (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hunc18a" encoded by a nucleic acid that hybridizes to the "Hunc18a" nucleic acid or its complement under low stringency conditions, and/or

(vii) "PAWR" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PAWR" encoded by a

nucleic acid that hybridizes to the "PAWR" nucleic acid or its complement under low stringency conditions, and/or

(viii) "STX1A" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1A" encoded by a nucleic acid that hybridizes to the "STX1A" nucleic acid or its complement under low stringency conditions, and/or

(ix) "STX1B2" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1B2" encoded by a nucleic acid that hybridizes to the "STX1B2" nucleic acid or its complement under low stringency conditions, and/or

(x) "STX3A" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX3A" encoded by a nucleic acid that hybridizes to the "STX3A" nucleic acid or its complement under low stringency conditions, and/or

(xi) "X11alpha" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11alpha" encoded by a nucleic acid that hybridizes to the "X11alpha" nucleic acid or its complement under low stringency conditions, and/or

(xii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders; .

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "ELAVL1" (SEQ ID No:105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ELAVL1" encoded by a nucleic acid that hybridizes to the "ELAVL1" nucleic acid or its complement under low stringency conditions,  
(ii) "Epim" (SEQ ID No:106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Epim" encoded by a nucleic acid that hybridizes to the "Epim" nucleic acid or its complement under low stringency conditions,  
(iii) "FIGF" (SEQ ID No:107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FIGF" encoded by a

nucleic acid that hybridizes to the "FIGF" nucleic acid or its complement under low stringency conditions,

(iv) "Filamin, gamma" (SEQ ID No:108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Filamin, gamma" encoded by a nucleic acid that hybridizes to the "Filamin, gamma" nucleic acid or its complement under low stringency conditions,

(v) "GOLGA3" (SEQ ID No:109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GOLGA3" encoded by a nucleic acid that hybridizes to the "GOLGA3" nucleic acid or its complement under low stringency conditions,

(vi) "Hunc18a" (SEQ ID No:110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hunc18a" encoded by a nucleic acid that hybridizes to the "Hunc18a" nucleic acid or its complement under low stringency conditions,

(vii) "PAWR" (SEQ ID No:111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PAWR" encoded by a nucleic acid that hybridizes to the "PAWR" nucleic acid or its complement under low stringency conditions,

(viii) "STX1A" (SEQ ID No:112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1A" encoded by a nucleic acid that hybridizes to the "STX1A" nucleic acid or its complement under low stringency conditions,

(ix) "STX1B2" (SEQ ID No:113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX1B2" encoded by a nucleic acid that hybridizes to the "STX1B2" nucleic acid or its complement under low stringency conditions,

(x) "STX3A" (SEQ ID No:114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX3A" encoded by a nucleic acid that hybridizes to the "STX3A" nucleic acid or its complement under low stringency conditions,

(xi) "X11alpha" (SEQ ID No:115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11alpha" encoded by a nucleic acid that hybridizes to the "X11alpha" nucleic acid or its complement under low stringency conditions,

(xii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or(xiii) "hypothetical protein BC013764" (SEQ ID No:116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hypothetical protein BC013764" encoded by a nucleic acid that hybridizes to the "hypothetical protein BC013764" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related disorders; .

The invention further relates to the following embodiments of the Telencephalin-complex

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "CD11a/CD18 INTEGRIN, BETA-2" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CD11a/CD18 INTEGRIN, BETA-2" encoded by a nucleic acid that hybridizes to the "CD11a/CD18 INTEGRIN, BETA-2" nucleic acid or its complement under low stringency conditions,
    - (ii) "Presenilin 1" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin 1" encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and
    - (iii) "Telencephalin" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Telencephalin" encoded by a nucleic acid that hybridizes to the "Telencephalin" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one second protein, which second protein is selected from the group consisting of:
    - (i) "APOD" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APOD" encoded by a



nucleic acid that hybridizes to the "APOD" nucleic acid or its complement under low stringency conditions,

(ii) "CALD1" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALD1" encoded by a nucleic acid that hybridizes to the "CALD1" nucleic acid or its complement under low stringency conditions,

(iii) "CALR" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALR" encoded by a nucleic acid that hybridizes to the "CALR" nucleic acid or its complement under low stringency conditions,

(iv) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,

(v) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,

(vi) "OPA1" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OPA1" encoded by a nucleic acid that hybridizes to the "OPA1" nucleic acid or its complement under low stringency conditions,

(vii) "PYCS" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PYCS" encoded by a nucleic acid that hybridizes to the "PYCS" nucleic acid or its complement under low stringency conditions,

(viii) "RAB6A" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB6A" encoded by a nucleic acid that hybridizes to the "RAB6A" nucleic acid or its complement under low stringency conditions, and

(ix) "RAP1, GTP-GDP dissociation stimulator 1" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAP1, GTP-GDP dissociation stimulator 1" encoded by a nucleic acid that

hybridizes to the "RAP1, GTP-GDP dissociation stimulator 1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Telencephalin (SEQ ID NO. 126), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Telencephalin' encoded by a nucleic acid that hybridizes to the 'Telencephalin' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "APOD" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APOD" encoded by a nucleic acid that hybridizes to the "APOD" nucleic acid or its complement under low stringency conditions,
- (ii) "CALD1" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALD1" encoded by a nucleic acid that hybridizes to the "CALD1" nucleic acid or its complement under low stringency conditions,
- (iii) "CALR" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALR" encoded by a nucleic acid that hybridizes to the "CALR" nucleic acid or its complement under low stringency conditions,
- (iv) "CD11a/CD18 INTEGRIN, BETA-2" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CD11a/CD18 INTEGRIN, BETA-2" encoded by a nucleic acid that hybridizes

to the "CD11a/CD18 INTEGRIN, BETA-2" nucleic acid or its complement under low stringency conditions,

(v) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,

(vi) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,

(vii) "OPA1" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OPA1" encoded by a nucleic acid that hybridizes to the "OPA1" nucleic acid or its complement under low stringency conditions,

(viii) "PYCS" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PYCS" encoded by a nucleic acid that hybridizes to the "PYCS" nucleic acid or its complement under low stringency conditions,

(ix) "Presenilin 1" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin 1" encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(x) "RAB6A" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB6A" encoded by a nucleic acid that hybridizes to the "RAB6A" nucleic acid or its complement under low stringency conditions,

(xi) "RAP1, GTP-GDP dissociation stimulator 1" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAP1, GTP-GDP dissociation stimulator 1" encoded by a nucleic acid that hybridizes to the "RAP1, GTP-GDP dissociation stimulator 1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Telencephalin" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Telencephalin"

encoded by a nucleic acid that hybridizes to the "Telencephalin" nucleic acid or its complement under low stringency conditions,

and a protein complex selected from complex (II) and comprising the following proteins:

- (i) "APOD" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APOD" encoded by a nucleic acid that hybridizes to the "APOD" nucleic acid or its complement under low stringency conditions,
- (ii) "CALD1" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALD1" encoded by a nucleic acid that hybridizes to the "CALD1" nucleic acid or its complement under low stringency conditions,
- (iii) "CALR" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALR" encoded by a nucleic acid that hybridizes to the "CALR" nucleic acid or its complement under low stringency conditions,
- (iv) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,
- (v) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,
- (vi) "OPA1" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OPA1" encoded by a nucleic acid that hybridizes to the "OPA1" nucleic acid or its complement under low stringency conditions,
- (vii) "PYCS" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PYCS" encoded by a nucleic acid that hybridizes to the "PYCS" nucleic acid or its complement under low stringency conditions,
- (viii) "RAB6A" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB6A"

encoded by a nucleic acid that hybridizes to the "RAB6A" nucleic acid or its complement under low stringency conditions,

(ix) "RAP1, GTP-GDP dissociation stimulator 1" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAP1, GTP-GDP dissociation stimulator 1" encoded by a nucleic acid that hybridizes to the "RAP1, GTP-GDP dissociation stimulator 1" nucleic acid or its complement under low stringency conditions, and/or

(x) "Telencephalin" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Telencephalin" encoded by a nucleic acid that hybridizes to the "Telencephalin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 8 of the following proteins:

(i) "APOD" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APOD" encoded by a nucleic acid that hybridizes to the "APOD" nucleic acid or its complement under low stringency conditions,

(ii) "CALD1" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALD1" encoded by a nucleic acid that hybridizes to the "CALD1" nucleic acid or its complement under low stringency conditions,

(iii) "CALR" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALR" encoded by a nucleic acid that hybridizes to the "CALR" nucleic acid or its complement under low stringency conditions,

(iv) "CD11a/CD18 INTEGRIN, BETA-2" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CD11a/CD18 INTEGRIN, BETA-2" encoded by a nucleic acid that hybridizes to the "CD11a/CD18 INTEGRIN, BETA-2" nucleic acid or its complement under low stringency conditions,

(v) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a

nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,

(vi) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,

(vii) "OPA1" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OPA1" encoded by a nucleic acid that hybridizes to the "OPA1" nucleic acid or its complement under low stringency conditions,

(viii) "PYCS" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PYCS" encoded by a nucleic acid that hybridizes to the "PYCS" nucleic acid or its complement under low stringency conditions,

(ix) "Presenilin 1" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin 1" encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(x) "RAB6A" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB6A" encoded by a nucleic acid that hybridizes to the "RAB6A" nucleic acid or its complement under low stringency conditions,

(xi) "RAP1, GTP-GDP dissociation stimulator 1" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAP1, GTP-GDP dissociation stimulator 1" encoded by a nucleic acid that hybridizes to the "RAP1, GTP-GDP dissociation stimulator 1" nucleic acid or its complement under low stringency conditions,

(xii) "Telencephalin" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Telencephalin" encoded by a nucleic acid that hybridizes to the "Telencephalin" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Telencephalin obtainable by a process according to any of No. 9 - 11.
13. Protein of the Telencephalin selected from
  - (i) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.
14. Nucleic acid encoding a protein according to No. 13.
15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
  - (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).



16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing Telencephalin to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "APOD" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APOD" encoded by a nucleic acid that hybridizes to the "APOD" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "CALD1" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALD1" encoded by a nucleic acid that hybridizes to the "CALD1" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "CALR" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALR" encoded by a nucleic acid that hybridizes to the "CALR" nucleic acid or its complement under low stringency conditions, and/or

- (iv) "CD11a/CD18 INTEGRIN, BETA-2" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CD11a/CD18 INTEGRIN, BETA-2" encoded by a nucleic acid that hybridizes to the "CD11a/CD18 INTEGRIN, BETA-2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "OPA1" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OPA1" encoded by a nucleic acid that hybridizes to the "OPA1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "PYCS" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PYCS" encoded by a nucleic acid that hybridizes to the "PYCS" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Presenilin 1" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin 1" encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or
- (x) "RAB6A" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB6A" encoded by a nucleic acid that hybridizes to the "RAB6A" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "RAP1, GTP-GDP dissociation stimulator 1" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAP1, GTP-GDP dissociation stimulator 1" encoded by a nucleic acid that

hybridizes to the "RAP1, GTP-GDP dissociation stimulator 1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Telencephalin" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Telencephalin" encoded by a nucleic acid that hybridizes to the "Telencephalin" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.
40. The method of No. 39, wherein said determining step comprises determining whether
- (i) "APOD" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APOD" encoded by a nucleic acid that hybridizes to the "APOD" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "CALD1" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALD1" encoded by a nucleic acid that hybridizes to the "CALD1" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "CALR" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALR" encoded by a nucleic acid that hybridizes to the "CALR" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "CD11a/CD18 INTEGRIN, BETA-2" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CD11a/CD18 INTEGRIN, BETA-2" encoded by a nucleic acid that hybridizes to the "CD11a/CD18 INTEGRIN, BETA-2" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a

nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions, and/or

(vi) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions, and/or

(vii) "OPA1" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OPA1" encoded by a nucleic acid that hybridizes to the "OPA1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "PYCS" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PYCS" encoded by a nucleic acid that hybridizes to the "PYCS" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Presenilin 1" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin 1" encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions, and/or

(x) "RAB6A" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB6A" encoded by a nucleic acid that hybridizes to the "RAB6A" nucleic acid or its complement under low stringency conditions, and/or

(xi) "RAP1, GTP-GDP dissociation stimulator 1" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAP1, GTP-GDP dissociation stimulator 1" encoded by a nucleic acid that hybridizes to the "RAP1, GTP-GDP dissociation stimulator 1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "Telencephalin" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Telencephalin" encoded by a nucleic acid that hybridizes to the "Telencephalin" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.
42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.
43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "APOD" (SEQ ID No:117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APOD" encoded by a nucleic acid that hybridizes to the "APOD" nucleic acid or its complement under low stringency conditions,



- (ii) "CALD1" (SEQ ID No:118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALD1" encoded by a nucleic acid that hybridizes to the "CALD1" nucleic acid or its complement under low stringency conditions,
- (iii) "CALR" (SEQ ID No:119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALR" encoded by a nucleic acid that hybridizes to the "CALR" nucleic acid or its complement under low stringency conditions,
- (iv) "CD11a/CD18 INTEGRIN, BETA-2" (SEQ ID No:120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CD11a/CD18 INTEGRIN, BETA-2" encoded by a nucleic acid that hybridizes to the "CD11a/CD18 INTEGRIN, BETA-2" nucleic acid or its complement under low stringency conditions,
- (v) "CHRNA5" (SEQ ID No:78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CHRNA5" encoded by a nucleic acid that hybridizes to the "CHRNA5" nucleic acid or its complement under low stringency conditions,
- (vi) "HYPOTHETICAL PROTEIN FLJ35393" (SEQ ID No:69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ35393" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ35393" nucleic acid or its complement under low stringency conditions,
- (vii) "OPA1" (SEQ ID No:121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OPA1" encoded by a nucleic acid that hybridizes to the "OPA1" nucleic acid or its complement under low stringency conditions,
- (viii) "PYCS" (SEQ ID No:122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PYCS" encoded by a nucleic acid that hybridizes to the "PYCS" nucleic acid or its complement under low stringency conditions,
- (ix) "Presenilin 1" (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin 1" encoded by a nucleic acid that hybridizes to the "Presenilin 1" nucleic acid or its complement under low stringency conditions,

(x) "RAB6A" (SEQ ID No:124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAB6A" encoded by a nucleic acid that hybridizes to the "RAB6A" nucleic acid or its complement under low stringency conditions,

(xi) "RAP1, GTP-GDP dissociation stimulator 1" (SEQ ID No:125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAP1, GTP-GDP dissociation stimulator 1" encoded by a nucleic acid that hybridizes to the "RAP1, GTP-GDP dissociation stimulator 1" nucleic acid or its complement under low stringency conditions, and/or(xii) "Telencephalin" (SEQ ID No:126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Telencephalin" encoded by a nucleic acid that hybridizes to the "Telencephalin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the following embodiments of the PC7-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and

(ii) "PC7" (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PC7" encoded by a nucleic acid that hybridizes to the "PC7" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "15 KDA SELENO- PROTEIN PRECURSOR" (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a

variant of "15 KDA SELENO- PROTEIN PRECURSOR" encoded by a nucleic acid that hybridizes to the "15 KDA SELENO- PROTEIN PRECURSOR" nucleic acid or its complement under low stringency conditions,

(ii) "APP-C99" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,

(iv) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(v) "PTPN1" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTPN1" encoded by a nucleic acid that hybridizes to the "PTPN1" nucleic acid or its complement under low stringency conditions, and

(vi) "Protocadherin beta 7 " (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7 " encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7 " nucleic acid or its complement under low stringency conditions, and a complex

(II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein PC7 (SEQ ID NO. 130), or a functionally active derivative thereof, or a functionally active

fragment thereof, or a homolog thereof, or a variant of 'PC7' encoded by a nucleic acid that hybridizes to the 'PC7' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "15 KDA SELENO- PROTEIN PRECURSOR" (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "15 KDA SELENO- PROTEIN PRECURSOR" encoded by a nucleic acid that hybridizes to the "15 KDA SELENO- PROTEIN PRECURSOR" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (iv) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,
- (v) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (vi) "PC7" (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PC7" encoded by a nucleic acid that hybridizes to the "PC7" nucleic acid or its complement under low stringency conditions,
- (vii) "PTPN1" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTPN1" encoded by a nucleic acid that hybridizes to the "PTPN1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Protocadherin beta 7 " (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7 " encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7 " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 5 of the following proteins:

- (i) "15 KDA SELENO- PROTEIN PRECURSOR" (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "15 KDA SELENO- PROTEIN PRECURSOR" encoded by a nucleic acid that hybridizes to the "15 KDA SELENO- PROTEIN PRECURSOR" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (iv) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,
- (v) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (vi) "PC7" (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PC7" encoded by a nucleic acid that hybridizes to the "PC7" nucleic acid or its complement under low stringency conditions,
- (vii) "PTPN1" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTPN1" encoded by a

nucleic acid that hybridizes to the "PTPN1" nucleic acid or its complement under low stringency conditions,

(viii) "Protocadherin beta 7 " (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7 " encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7 " nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the PC7 obtainable by a process according to any of No. 9 - 11.
13. Protein of the PC7 selected from
  - (i) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and
  - (ii) "Protocadherin beta 7" (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7" encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.
14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or  
(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.
18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
19. The kit according to No. 18 for processing a substrate of said complex.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders; .



21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Protocadherin beta 7 " (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7 " encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7 " nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders; .

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Protocadherin beta 7 " (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7 " encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7 " nucleic acid or its complement under low stringency conditions, comprising the steps of

- (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing PC7 to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of

said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "15 KDA SELENO- PROTEIN PRECURSOR" (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "15 KDA SELENO- PROTEIN PRECURSOR" encoded by a nucleic acid that hybridizes to the "15 KDA SELENO- PROTEIN PRECURSOR" nucleic acid or its

complement under low stringency conditions, and/or

(ii) "APP-C99" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(iii) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and/or

(v) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(vi) "PC7" (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PC7" encoded by a nucleic acid that hybridizes to the "PC7" nucleic acid or its complement under low stringency conditions, and/or

(vii) "PTPN1" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTPN1" encoded by a

nucleic acid that hybridizes to the "PTPN1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Protocadherin beta 7 " (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7 " encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7 " nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders; .

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders; .

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.
40. The method of No. 39, wherein said determining step comprises determining whether
- (i) "15 KDA SELENO- PROTEIN PRECURSOR" (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "15 KDA SELENO- PROTEIN PRECURSOR" encoded by a nucleic acid that hybridizes to the "15 KDA SELENO- PROTEIN PRECURSOR" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APP-C99" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions, and/or

- (v) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "PC7" (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PC7" encoded by a nucleic acid that hybridizes to the "PC7" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "PTPN1" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTPN1" encoded by a nucleic acid that hybridizes to the "PTPN1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Protocadherin beta 7 " (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7 " encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7 " nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders; .

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of

beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "15 KDA SELENO- PROTEIN PRECURSOR" (SEQ ID No:127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "15 KDA SELENO- PROTEIN PRECURSOR" encoded by a nucleic acid that hybridizes to the "15 KDA SELENO- PROTEIN PRECURSOR" nucleic acid or its complement under low stringency conditions,

(ii) "APP-C99" (SEQ ID No:128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,

(iv) "DNAJC3" (SEQ ID No:82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DNAJC3" encoded by a nucleic acid that hybridizes to the "DNAJC3" nucleic acid or its complement under low stringency conditions,

(v) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin"

encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(vi) "PC7" (SEQ ID No:130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PC7" encoded by a nucleic acid that hybridizes to the "PC7" nucleic acid or its complement under low stringency conditions,

(vii) "PTPN1" (SEQ ID No:131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTPN1" encoded by a nucleic acid that hybridizes to the "PTPN1" nucleic acid or its complement under low stringency conditions, and/or(viii) "Protocadherin beta 7 " (SEQ ID No:132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Protocadherin beta 7 " encoded by a nucleic acid that hybridizes to the "Protocadherin beta 7 " nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders; .

The invention further relates to the following embodiments of the VTRP-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "BET1" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BET1" encoded by a nucleic acid that hybridizes to the "BET1" nucleic acid or its complement under low stringency conditions,

(ii) "SYNTAXIN 18" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 18" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 18" nucleic acid or its complement under low stringency conditions,

(iii) "SYNTAXIN 5" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 5"



encoded by a nucleic acid that hybridizes to the "SYNTAXIN 5" nucleic acid or its complement under low stringency conditions, and

(iv) "VTRP" (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VTRP" encoded by a nucleic acid that hybridizes to the "VTRP" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "27 KDA GOLGI SNARE PROTEIN" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "27 KDA GOLGI SNARE PROTEIN" encoded by a nucleic acid that hybridizes to the "27 KDA GOLGI SNARE PROTEIN" nucleic acid or its complement under low stringency conditions,

(ii) "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" encoded by a nucleic acid that hybridizes to the "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" nucleic acid or its complement under low stringency conditions,

(iii) "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" encoded by a nucleic acid that hybridizes to the "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" nucleic acid or its complement under low stringency conditions,

(iv) "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" encoded by a nucleic acid that hybridizes to the "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" nucleic acid or its complement under low stringency conditions,

(v) "CALPAIN SMALL SUBUNIT" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALPAIN SMALL SUBUNIT" encoded by a nucleic acid that hybridizes to the "CALPAIN SMALL SUBUNIT" nucleic acid or its complement under low stringency conditions,

- (vi) "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" encoded by a nucleic acid that hybridizes to the "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" nucleic acid or its complement under low stringency conditions,
- (vii) "DYNAMACTIN COMPLEX 50 KDA SUBUNIT" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DYNAMACTIN COMPLEX 50 KDA SUBUNIT" encoded by a nucleic acid that hybridizes to the "DYNAMACTIN COMPLEX 50 KDA SUBUNIT" nucleic acid or its complement under low stringency conditions,
- (viii) "GP25L2 PROTEIN" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GP25L2 PROTEIN" encoded by a nucleic acid that hybridizes to the "GP25L2 PROTEIN" nucleic acid or its complement under low stringency conditions,
- (ix) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009" encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions,
- (x) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xi) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xii) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED

HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions,

(xiii) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions,

(xiv) "Phosphatidylserine receptor" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Phosphatidylserine receptor" encoded by a nucleic acid that hybridizes to the "Phosphatidylserine receptor" nucleic acid or its complement under low stringency conditions,

(xv) "RAD50-INTERACTING PROTEIN 1" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAD50-INTERACTING PROTEIN 1" encoded by a nucleic acid that hybridizes to the "RAD50-INTERACTING PROTEIN 1" nucleic acid or its complement under low stringency conditions,

(xvi) "SEC22B VESICLE TRAFFICKING PROTEIN" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SEC22B VESICLE TRAFFICKING PROTEIN" encoded by a nucleic acid that hybridizes to the "SEC22B VESICLE TRAFFICKING PROTEIN" nucleic acid or its complement under low stringency conditions,

(xvii) "SYNTAXIN 10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 10" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 10" nucleic acid or its complement under low stringency conditions,

(xviii) "Similar to golgi SNAP receptor complex member 1" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to golgi SNAP receptor complex member 1" encoded by a nucleic acid that hybridizes to the "Similar to golgi SNAP receptor complex member 1" nucleic acid or its complement under low stringency conditions,

(xix) "Vesicular fusion protein - NSFS" (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Vesicular fusion protein - NSF" encoded by a nucleic acid that hybridizes to the

"Vesicular fusion protein - NSF" nucleic acid or its complement under low stringency conditions,

and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein VTRP (SEQ ID NO. 155), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'VTRP' encoded by a nucleic acid that hybridizes to the 'VTRP' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

(i) "27 KDA GOLGI SNARE PROTEIN" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "27 KDA GOLGI SNARE PROTEIN" encoded by a nucleic acid that hybridizes to the "27 KDA GOLGI SNARE PROTEIN" nucleic acid or its complement under low stringency conditions,

(ii) "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" encoded by a nucleic acid that hybridizes to the "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" nucleic acid or its complement under low stringency conditions,

(iii) "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" encoded by a nucleic acid that hybridizes to the "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" nucleic acid or its complement under low stringency conditions,

- (iv) "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" encoded by a nucleic acid that hybridizes to the "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" nucleic acid or its complement under low stringency conditions,
- (v) "BET1" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BET1" encoded by a nucleic acid that hybridizes to the "BET1" nucleic acid or its complement under low stringency conditions,
- (vi) "CALPAIN SMALL SUBUNIT" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALPAIN SMALL SUBUNIT" encoded by a nucleic acid that hybridizes to the "CALPAIN SMALL SUBUNIT" nucleic acid or its complement under low stringency conditions,
- (vii) "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" encoded by a nucleic acid that hybridizes to the "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" nucleic acid or its complement under low stringency conditions,
- (viii) "DYNACTIN COMPLEX 50 KDA SUBUNIT" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DYNACTIN COMPLEX 50 KDA SUBUNIT" encoded by a nucleic acid that hybridizes to the "DYNACTIN COMPLEX 50 KDA SUBUNIT" nucleic acid or its complement under low stringency conditions,
- (ix) "GP25L2 PROTEIN" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GP25L2 PROTEIN" encoded by a nucleic acid that hybridizes to the "GP25L2 PROTEIN" nucleic acid or its complement under low stringency conditions,
- (x) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009" encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions,

(xi) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xii) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xiii) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions,

(xiv) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions,

(xv) "Phosphatidylserine receptor" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Phosphatidylserine receptor" encoded by a nucleic acid that hybridizes to the "Phosphatidylserine receptor" nucleic acid or its complement under low stringency conditions,

(xvi) "RAD50-INTERACTING PROTEIN 1" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAD50-INTERACTING PROTEIN 1" encoded by a nucleic acid that hybridizes to the "RAD50-INTERACTING PROTEIN 1" nucleic acid or its complement under low stringency conditions,

(xvii) "SEC22B VESICLE TRAFFICKING PROTEIN" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof,

or a variant of "SEC22B VESICLE TRAFFICKING PROTEIN" encoded by a nucleic acid that hybridizes to the "SEC22B VESICLE TRAFFICKING PROTEIN" nucleic acid or its complement under low stringency conditions,

(xviii) "SYNTAXIN 10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 10" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 10" nucleic acid or its complement under low stringency conditions,

(xix) "SYNTAXIN 18" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 18" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 18" nucleic acid or its complement under low stringency conditions,

(xx) "SYNTAXIN 5" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 5" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 5" nucleic acid or its complement under low stringency conditions,

(xxi) "Similar to golgi SNAP receptor complex member 1" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to golgi SNAP receptor complex member 1" encoded by a nucleic acid that hybridizes to the "Similar to golgi SNAP receptor complex member 1" nucleic acid or its complement under low stringency conditions,

(xxii) "VESICULAR-FUSION PROTEIN NSF" (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR-FUSION PROTEIN NSF" encoded by a nucleic acid that hybridizes to the "VESICULAR-FUSION PROTEIN NSF" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "VTRP" (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VTRP" encoded by a nucleic acid that hybridizes to the "VTRP" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 17 of the following proteins:

(i) "27 KDA GOLGI SNARE PROTEIN" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a

variant of "27 KDA GOLGI SNARE PROTEIN" encoded by a nucleic acid that hybridizes to the "27 KDA GOLGI SNARE PROTEIN" nucleic acid or its complement under low stringency conditions,

(ii) "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" encoded by a nucleic acid that hybridizes to the "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" nucleic acid or its complement under low stringency conditions,

(iii) "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" encoded by a nucleic acid that hybridizes to the "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" nucleic acid or its complement under low stringency conditions,

(iv) "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" encoded by a nucleic acid that hybridizes to the "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" nucleic acid or its complement under low stringency conditions,

(v) "BET1" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BET1" encoded by a nucleic acid that hybridizes to the "BET1" nucleic acid or its complement under low stringency conditions,

(vi) "CALPAIN SMALL SUBUNIT" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALPAIN SMALL SUBUNIT" encoded by a nucleic acid that hybridizes to the "CALPAIN SMALL SUBUNIT" nucleic acid or its complement under low stringency conditions,

(vii) "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" encoded by a nucleic acid that hybridizes to the "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" nucleic acid or its complement under low stringency conditions,



- (viii) "DYNACTIN COMPLEX 50 KDA SUBUNIT" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DYNACTIN COMPLEX 50 KDA SUBUNIT" encoded by a nucleic acid that hybridizes to the "DYNACTIN COMPLEX 50 KDA SUBUNIT" nucleic acid or its complement under low stringency conditions,
- (ix) "GP25L2 PROTEIN" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GP25L2 PROTEIN" encoded by a nucleic acid that hybridizes to the "GP25L2 PROTEIN" nucleic acid or its complement under low stringency conditions,
- (x) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009" encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions,
- (xi) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xii) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions,
- (xiv) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid

that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions,

(xv) "Phosphatidylserine receptor" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Phosphatidylserine receptor" encoded by a nucleic acid that hybridizes to the "Phosphatidylserine receptor" nucleic acid or its complement under low stringency conditions,

(xvi) "RAD50-INTERACTING PROTEIN 1" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAD50-INTERACTING PROTEIN 1" encoded by a nucleic acid that hybridizes to the "RAD50-INTERACTING PROTEIN 1" nucleic acid or its complement under low stringency conditions,

(xvii) "SEC22B VESICLE TRAFFICKING PROTEIN" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SEC22B VESICLE TRAFFICKING PROTEIN" encoded by a nucleic acid that hybridizes to the "SEC22B VESICLE TRAFFICKING PROTEIN" nucleic acid or its complement under low stringency conditions,

(xviii) "SYNTAXIN 10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 10" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 10" nucleic acid or its complement under low stringency conditions,

(xix) "SYNTAXIN 18" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 18" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 18" nucleic acid or its complement under low stringency conditions,

(xx) "SYNTAXIN 5" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 5" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 5" nucleic acid or its complement under low stringency conditions,

(xxi) "Similar to golgi SNAP receptor complex member 1" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to golgi SNAP receptor complex member 1" encoded by a nucleic acid that hybridizes to the "Similar to golgi SNAP receptor complex member 1" nucleic acid or its complement under low stringency conditions,

(xxii) "VESICULAR-FUSION PROTEIN NSF" (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR-FUSION PROTEIN NSF" encoded by a nucleic acid that hybridizes to the "VESICULAR-FUSION PROTEIN NSF" nucleic acid or its complement under low stringency conditions,

(xxiii) "VTRP" (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VTRP" encoded by a nucleic acid that hybridizes to the "VTRP" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by

modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the VTRP complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the VTRP complex selected from

- (i) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009" encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions,
- (ii) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (iii) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(iv) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions, and

(v) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the

nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009"

encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions,

(ii) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(iii) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(iv) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(v) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease;

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009"

encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions,

(ii) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(iii) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(iv) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(v) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing VTRP complex to one or more candidate molecules; and



(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether  
 (i) "27 KDA GOLGI SNARE PROTEIN" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "27 KDA GOLGI SNARE PROTEIN" encoded by a nucleic acid that hybridizes to the "27 KDA GOLGI SNARE PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(ii) "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN"

encoded by a nucleic acid that hybridizes to the "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(iii) "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1"

(SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AMYLOID BETA A4

PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" encoded by a nucleic acid that hybridizes to the "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY

B MEMBER 1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1"

(SEQ ID No:136) or a functionally active derivative thereof, or a functionally active

fragment thereof, or a homolog thereof, or a variant of "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" encoded by a nucleic acid that

hybridizes to the "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1,

ISOFORM BNIP1" nucleic acid or its complement under low stringency conditions,

and/or

(v) "BET1" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally

active fragment thereof, or a homolog thereof, or a variant of "BET1" encoded by a

nucleic acid that hybridizes to the "BET1" nucleic acid or its complement under low

stringency conditions, and/or

(vi) "CALPAIN SMALL SUBUNIT" (SEQ ID No:138) or a functionally active derivative

thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"CALPAIN SMALL SUBUNIT" encoded by a nucleic acid that hybridizes to the "CALPAIN

SMALL SUBUNIT" nucleic acid or its complement under low stringency conditions,

and/or

(vii) "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" (SEQ ID No:139)

or a functionally active derivative thereof, or a functionally active fragment thereof, or a

homolog thereof, or a variant of "CENTROMERE/KINETOCHORE PROTEIN ZW10

HOMOLOG" encoded by a nucleic acid that hybridizes to the

"CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" nucleic acid or its

complement under low stringency conditions, and/or

(viii) "DYNAMACTIN COMPLEX 50 KDA SUBUNIT" (SEQ ID No:140) or a functionally

active derivative thereof, or a functionally active fragment thereof, or a homolog thereof,

or a variant of "DYNAMACTIN COMPLEX 50 KDA SUBUNIT" encoded by a nucleic acid

that hybridizes to the "DYNACTIN COMPLEX 50 KDA SUBUNIT" nucleic acid or its complement under low stringency conditions, and/or

(ix) "GP25L2 PROTEIN" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GP25L2 PROTEIN" encoded by a nucleic acid that hybridizes to the "GP25L2 PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(x) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009" encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions, and/or

(xi) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xii) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Phosphatidylserine receptor" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"Phosphatidylserine receptor" encoded by a nucleic acid that hybridizes to the "Phosphatidylserine receptor" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "RAD50-INTERACTING PROTEIN 1" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAD50-INTERACTING PROTEIN 1" encoded by a nucleic acid that hybridizes to the "RAD50-INTERACTING PROTEIN 1" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "SEC22B VESICLE TRAFFICKING PROTEIN" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SEC22B VESICLE TRAFFICKING PROTEIN" encoded by a nucleic acid that hybridizes to the "SEC22B VESICLE TRAFFICKING PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "SYNTAXIN 10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 10" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 10" nucleic acid or its complement under low stringency conditions, and/or

(xix) "SYNTAXIN 18" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 18" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 18" nucleic acid or its complement under low stringency conditions, and/or

(xx) "SYNTAXIN 5" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 5" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 5" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Similar to golgi SNAP receptor complex member 1" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to golgi SNAP receptor complex member 1" encoded by a nucleic acid that hybridizes to the "Similar to golgi SNAP receptor complex member 1" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "VESICULAR-FUSION PROTEIN NSF" (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR-FUSION PROTEIN NSF" encoded by a nucleic acid that

hybridizes to the "VESICULAR-FUSION PROTEIN NSF" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "VTRP" (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VTRP" encoded by a nucleic acid that hybridizes to the "VTRP" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether  
(i) "27 KDA GOLGI SNARE PROTEIN" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "27 KDA GOLGI SNARE PROTEIN" encoded by a nucleic acid that hybridizes to the "27 KDA GOLGI SNARE PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(ii) "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" encoded by a nucleic acid that hybridizes to the "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(iii) "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" encoded by a nucleic acid that hybridizes to the "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BCL2/ADENOVIRUS E1B 19KD-

INTERACTING PROTEIN 1, ISOFORM BNIP1" encoded by a nucleic acid that hybridizes to the "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" nucleic acid or its complement under low stringency conditions, and/or

(v) "BET1" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BET1" encoded by a nucleic acid that hybridizes to the "BET1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CALPAIN SMALL SUBUNIT" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALPAIN SMALL SUBUNIT" encoded by a nucleic acid that hybridizes to the "CALPAIN SMALL SUBUNIT" nucleic acid or its complement under low stringency conditions, and/or

(vii) "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" encoded by a nucleic acid that hybridizes to the "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" nucleic acid or its complement under low stringency conditions, and/or

(viii) "DYNAMACTIN COMPLEX 50 KDA SUBUNIT" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DYNAMACTIN COMPLEX 50 KDA SUBUNIT" encoded by a nucleic acid that hybridizes to the "DYNAMACTIN COMPLEX 50 KDA SUBUNIT" nucleic acid or its complement under low stringency conditions, and/or

(ix) "GP25L2 PROTEIN" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GP25L2 PROTEIN" encoded by a nucleic acid that hybridizes to the "GP25L2 PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(x) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009" encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions, and/or

(xi) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof,

or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xii) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xv) "Phosphatidylserine receptor" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Phosphatidylserine receptor" encoded by a nucleic acid that hybridizes to the "Phosphatidylserine receptor" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "RAD50-INTERACTING PROTEIN 1" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAD50-INTERACTING PROTEIN 1" encoded by a nucleic acid that hybridizes to the "RAD50-INTERACTING PROTEIN 1" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "SEC22B VESICLE TRAFFICKING PROTEIN" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SEC22B VESICLE TRAFFICKING PROTEIN" encoded by a nucleic acid



that hybridizes to the "SEC22B VESICLE TRAFFICKING PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "SYNTAXIN 10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 10" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 10" nucleic acid or its complement under low stringency conditions, and/or

(xix) "SYNTAXIN 18" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 18" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 18" nucleic acid or its complement under low stringency conditions, and/or

(xx) "SYNTAXIN 5" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 5" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 5" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Similar to golgi SNAP receptor complex member 1" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to golgi SNAP receptor complex member 1" encoded by a nucleic acid that hybridizes to the "Similar to golgi SNAP receptor complex member 1" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "VESICULAR-FUSION PROTEIN NSF" (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR-FUSION PROTEIN NSF" encoded by a nucleic acid that hybridizes to the "VESICULAR-FUSION PROTEIN NSF" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "VTRP" (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VTRP" encoded by a nucleic acid that hybridizes to the "VTRP" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "27 KDA GOLGI SNARE PROTEIN" (SEQ ID No:133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "27 KDA GOLGI SNARE PROTEIN" encoded by a nucleic acid that hybridizes to the "27 KDA GOLGI SNARE PROTEIN" nucleic acid or its complement under low stringency conditions,  
(ii) "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" (SEQ ID No:134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" encoded by a nucleic acid that hybridizes to the "ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN" nucleic acid or its complement under low stringency conditions,

- (iii) "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" encoded by a nucleic acid that hybridizes to the "AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1" nucleic acid or its complement under low stringency conditions,
- (iv) "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" (SEQ ID No:136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" encoded by a nucleic acid that hybridizes to the "BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1" nucleic acid or its complement under low stringency conditions,
- (v) "BET1" (SEQ ID No:137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BET1" encoded by a nucleic acid that hybridizes to the "BET1" nucleic acid or its complement under low stringency conditions,
- (vi) "CALPAIN SMALL SUBUNIT" (SEQ ID No:138) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CALPAIN SMALL SUBUNIT" encoded by a nucleic acid that hybridizes to the "CALPAIN SMALL SUBUNIT" nucleic acid or its complement under low stringency conditions,
- (vii) "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" (SEQ ID No:139) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" encoded by a nucleic acid that hybridizes to the "CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG" nucleic acid or its complement under low stringency conditions,
- (viii) "DYNACTIN COMPLEX 50 KDA SUBUNIT" (SEQ ID No:140) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DYNACTIN COMPLEX 50 KDA SUBUNIT" encoded by a nucleic acid that hybridizes to the "DYNACTIN COMPLEX 50 KDA SUBUNIT" nucleic acid or its complement under low stringency conditions,
- (ix) "GP25L2 PROTEIN" (SEQ ID No:141) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GP25L2

PROTEIN" encoded by a nucleic acid that hybridizes to the "GP25L2 PROTEIN" nucleic acid or its complement under low stringency conditions,

(x) "HSPC009" (SEQ ID No:142) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC009" encoded by a nucleic acid that hybridizes to the "HSPC009" nucleic acid or its complement under low stringency conditions,

(xi) "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" (SEQ ID No:143) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 61.5 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xii) "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" (SEQ ID No:144) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTH 78.2 KDA PROTEIN (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xiii) "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" (SEQ ID No:145) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" encoded by a nucleic acid that hybridizes to the "MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN" nucleic acid or its complement under low stringency conditions,

(xiv) "NEUROBLASTOMA-AMPLIFIED PROTEIN" (SEQ ID No:146) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NEUROBLASTOMA-AMPLIFIED PROTEIN" encoded by a nucleic acid that hybridizes to the "NEUROBLASTOMA-AMPLIFIED PROTEIN" nucleic acid or its complement under low stringency conditions,

(xv) "Phosphatidylserine receptor" (SEQ ID No:147) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Phosphatidylserine receptor" encoded by a nucleic acid that hybridizes to the "Phosphatidylserine receptor" nucleic acid or its complement under low stringency conditions,

- (xvi) "RAD50-INTERACTING PROTEIN 1" (SEQ ID No:148) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RAD50-INTERACTING PROTEIN 1" encoded by a nucleic acid that hybridizes to the "RAD50-INTERACTING PROTEIN 1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SEC22B VESICLE TRAFFICKING PROTEIN" (SEQ ID No:149) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SEC22B VESICLE TRAFFICKING PROTEIN" encoded by a nucleic acid that hybridizes to the "SEC22B VESICLE TRAFFICKING PROTEIN" nucleic acid or its complement under low stringency conditions,
- (xviii) "SYNTAXIN 10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 10" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 10" nucleic acid or its complement under low stringency conditions,
- (xix) "SYNTAXIN 18" (SEQ ID No:151) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 18" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 18" nucleic acid or its complement under low stringency conditions,
- (xx) "SYNTAXIN 5" (SEQ ID No:152) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SYNTAXIN 5" encoded by a nucleic acid that hybridizes to the "SYNTAXIN 5" nucleic acid or its complement under low stringency conditions,
- (xxi) "Similar to golgi SNAP receptor complex member 1" (SEQ ID No:153) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to golgi SNAP receptor complex member 1" encoded by a nucleic acid that hybridizes to the "Similar to golgi SNAP receptor complex member 1" nucleic acid or its complement under low stringency conditions,
- (xxii) "VESICULAR-FUSION PROTEIN NSF" (SEQ ID No:154) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR-FUSION PROTEIN NSF" encoded by a nucleic acid that hybridizes to the "VESICULAR-FUSION PROTEIN NSF" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "VTRP" (SEQ ID No:155) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VTRP" encoded by a nucleic acid that hybridizes to the "VTRP" nucleic

acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

The invention further relates to the following embodiments of the Bace1-complex

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and
    - (ii) "Nicastrin" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one second protein, which second protein is selected from the group consisting of:
    - (i) "CGI-13" (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13" encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
    - (ii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
    - (iii) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,
    - (iv) "Delta-6 fatty acid desaturase" (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

- "Delta-6 fatty acid desaturase " encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions,
- (v) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions,
- (vii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249" encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions,
- (viii) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions,
- (ix) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250" encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
- (x) "Nogo-A" (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo-A" encoded by a nucleic acid that hybridizes to the "Nogo-A" nucleic acid or its complement under low stringency conditions,
- (xi) "PDGFRB" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,
- (xii) "PTK7" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,

- (xiii) "SERPINA1" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SERPINA1" encoded by a nucleic acid that hybridizes to the "SERPINA1" nucleic acid or its complement under low stringency conditions,
- (xiv) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions,
- (xv) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions,
- (xvi) "Sortilin-related receptor" (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Sortilin-related receptor" encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor" nucleic acid or its complement under low stringency conditions,
- (xvii) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,
- (xviii) "integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and
- (xix) "kinectin 1 (kinesin receptor)" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "kinectin 1 (kinesin receptor)" encoded by a nucleic acid that hybridizes to the "kinectin 1 (kinesin receptor)" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40



Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Bace1 (SEQ ID NO. 129), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Bace1' encoded by a nucleic acid that hybridizes to the 'Bace1' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

(i) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,

(ii) "CGI-13" (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13" encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

(iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,

(iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,

(v) "Delta-6 fatty acid desaturase " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-6 fatty acid desaturase " encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions,

- (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,
- (vii) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions,
- (viii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249" encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions,
- (ix) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions,
- (x) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250" encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
- (xi) "Nicastrin" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (xii) "Nogo-A" (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo-A" encoded by a nucleic acid that hybridizes to the "Nogo-A" nucleic acid or its complement under low stringency conditions,
- (xiii) "PDGFRB" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,
- (xiv) "PTK7" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a

nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,

(xv) "SERPINA1" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SERPINA1" encoded by a nucleic acid that hybridizes to the "SERPINA1" nucleic acid or its complement under low stringency conditions,

(xvi) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions,

(xvii) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions,

(xviii) "Sortilin-related receptor" (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Sortilin-related receptor" encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor" nucleic acid or its complement under low stringency conditions,

(xix) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,

(xx) "integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "kinectin 1 (kinesin receptor)" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "kinectin 1 (kinesin receptor)" encoded by a nucleic acid that hybridizes to the "kinectin 1 (kinesin receptor)" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 18 of the following proteins:

- (i) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (ii) "CGI-13" (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13" encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
- (iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,
- (v) "Delta-6 fatty acid desaturase " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-6 fatty acid desaturase " encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions,
- (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,
- (vii) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions,
- (viii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249"

encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions,

(ix) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions,

(x) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250" encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,

(xi) "Nicastrin" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(xii) "Nogo-A" (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo-A" encoded by a nucleic acid that hybridizes to the "Nogo-A" nucleic acid or its complement under low stringency conditions,

(xiii) "PDGFRB" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,

(xiv) "PTK7" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,

(xv) "SERPINA1" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SERPINA1" encoded by a nucleic acid that hybridizes to the "SERPINA1" nucleic acid or its complement under low stringency conditions,

(xvi) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions,

(xvii) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions,

(xviii) "Sortilin-related receptor" (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Sortilin-related receptor" encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor" nucleic acid or its complement under low stringency conditions,

(xix) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,

(xx) "integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,

(xxi) "kinectin 1 (kinesin receptor)" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "kinectin 1 (kinesin receptor)" encoded by a nucleic acid that hybridizes to the "kinectin 1 (kinesin receptor)" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the BACE1 complex obtainable by a process according to any of No. 9 - 11.
13. Protein of the BACE1 complex selected from

- (i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions,
- (iii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249" encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions,
- (iv) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250" encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
- (v) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions, and
- (vi) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.



15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or  
(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.
18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.
21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.
22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
  - (ii) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions,
  - (iii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249" encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions,
  - (iv) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250" encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
  - (v) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO

Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,

(ii) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions,

(iii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249" encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions,

(iv) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250" encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,

(v) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing BACE1 complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "CGI-13" (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13" encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions, and/or

(v) "Delta-6 fatty acid desaturase " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-6 fatty acid desaturase " encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions, and/or

(vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like

- homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions, and/or
  - (viii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249" encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions, and/or
  - (ix) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions, and/or
  - (x) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250" encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions, and/or
  - (xi) "Nicastrin" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
  - (xii) "Nogo-A" (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo-A" encoded by a nucleic acid that hybridizes to the "Nogo-A" nucleic acid or its complement under low stringency conditions, and/or
  - (xiii) "PDGFRB" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions, and/or
  - (xiv) "PTK7" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or

- (xv) "SERPINA1" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SERPINA1" encoded by a nucleic acid that hybridizes to the "SERPINA1" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "Sortilin-related receptor" (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Sortilin-related receptor" encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "kinectin 1 (kinesin receptor)" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "kinectin 1 (kinesin receptor)" encoded by a nucleic acid that hybridizes to the "kinectin 1 (kinesin receptor)" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.
34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said



complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "CGI-13" (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13" encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions, and/or

(v) "Delta-6 fatty acid desaturase " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-6 fatty acid desaturase " encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions, and/or

(vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions, and/or

- (vii) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249" encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions, and/or
- (x) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250" encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "Nicastrin" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Nogo-A" (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo-A" encoded by a nucleic acid that hybridizes to the "Nogo-A" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "PDGFRB" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "PTK7" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "SERPINA1" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SERPINA1"

encoded by a nucleic acid that hybridizes to the "SERPINA1" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "Sortilin-related receptor" (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Sortilin-related receptor" encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor" nucleic acid or its complement under low stringency conditions, and/or

(xix) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and/or

(xx) "integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "kinectin 1 (kinesin receptor)" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "kinectin 1 (kinesin receptor)" encoded by a nucleic acid that hybridizes to the "kinectin 1 (kinesin receptor)" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as

neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.
43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins
  - (i) "BACE1" (SEQ ID No:129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
  - (ii) "CGI-13" (SEQ ID No:156) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13" encoded by a

nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,

- (iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
- (iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,
- (v) "Delta-6 fatty acid desaturase " (SEQ ID No:159) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-6 fatty acid desaturase " encoded by a nucleic acid that hybridizes to the "Delta-6 fatty acid desaturase " nucleic acid or its complement under low stringency conditions,
- (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,
- (vii) "FLJ30668" (SEQ ID No:161) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ30668" encoded by a nucleic acid that hybridizes to the "FLJ30668" nucleic acid or its complement under low stringency conditions,
- (viii) "FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ39249" encoded by a nucleic acid that hybridizes to the "FLJ39249" nucleic acid or its complement under low stringency conditions,
- (ix) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions,
- (x) "KIAA1250" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250"

- encoded by a nucleic acid that hybridizes to the "KIAA1250" nucleic acid or its complement under low stringency conditions,
- (xi) "Nicastrin" (SEQ ID No:165) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (xii) "Nogo-A" (SEQ ID No:166) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo-A" encoded by a nucleic acid that hybridizes to the "Nogo-A" nucleic acid or its complement under low stringency conditions,
- (xiii) "PDGFRB" (SEQ ID No:167) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,
- (xiv) "PTK7" (SEQ ID No:168) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
- (xv) "SERPINA1" (SEQ ID No:169) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SERPINA1" encoded by a nucleic acid that hybridizes to the "SERPINA1" nucleic acid or its complement under low stringency conditions,
- (xvi) "SIM TO Y71H10A. 2.P" (SEQ ID No:170) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIM TO Y71H10A. 2.P" encoded by a nucleic acid that hybridizes to the "SIM TO Y71H10A. 2.P" nucleic acid or its complement under low stringency conditions,
- (xvii) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions,
- (xviii) "Sortilin-related receptor" (SEQ ID No:171) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Sortilin-related receptor" encoded by a nucleic acid that hybridizes to the "Sortilin-related receptor" nucleic acid or its complement under low stringency conditions,

(xix) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,

(xx) "integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and/or (xxi) "kinectin 1 (kinesin receptor)" (SEQ ID No:174) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "kinectin 1 (kinesin receptor)" encoded by a nucleic acid that hybridizes to the "kinectin 1 (kinesin receptor)" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further relates to the following embodiments of the Bace2-complex

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "BACE2" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one second protein, which second protein is selected from the group consisting of:
    - (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

- (ii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
- (iii) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,
- (iv) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,
- (v) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474" encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions,
- (vii) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions,
- (viii) "Integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,
- (ix) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and



(x) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Bace2 (SEQ ID NO. 175), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Bace2' encoded by a nucleic acid that hybridizes to the 'Bace2' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (ii) "BACE2" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
- (iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
- (iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1"

encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,

(v) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,

(vi) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474" encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions,

(vii) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions,

(viii) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions,

(ix) "Integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,

(x) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949

(FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xi) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 9 of the following proteins:

- (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (ii) "BACE2" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
- (iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
- (iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,
- (v) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474" encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions,
- (vii) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions,
- (viii) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions,

(ix) "Integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,

(x) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xi) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP

fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the BACE2 obtainable by a process according to any of No. 9 - 11.

13. Protein of the BACE2 selected from

- (i) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474" encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions, and
- (iii) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949

(FRAGMENT)" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and

an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474" encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949

(FRAGMENT)" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease;

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474" encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions,
- (ii) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, comprising the steps of
  - (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing BACE2 to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the



complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "BACE2" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a

homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions, and/or

(v) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions, and/or

(vi) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474" encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions, and/or

(vii) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions, and/or

(viii) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and/or

(x) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xi) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a

nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether  
(i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "BACE2" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1" encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions, and/or

(v) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions, and/or

(vi) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474"

encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions, and/or

(vii) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions, and/or

(viii) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions, and/or

(x) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xi) "STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying

the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(ii) "BACE2" (SEQ ID No:175) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,

(iii) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,

(iv) "Calsyntenin 1" (SEQ ID No:158) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Calsyntenin 1"

encoded by a nucleic acid that hybridizes to the "Calsyntenin 1" nucleic acid or its complement under low stringency conditions,

(v) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,

(vi) "FLJ10474" (SEQ ID No:176) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10474" encoded by a nucleic acid that hybridizes to the "FLJ10474" nucleic acid or its complement under low stringency conditions,

(vii) "FLJ14787" (SEQ ID No:177) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ14787" encoded by a nucleic acid that hybridizes to the "FLJ14787" nucleic acid or its complement under low stringency conditions,

(viii) "ITCH" (SEQ ID No:163) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITCH" encoded by a nucleic acid that hybridizes to the "ITCH" nucleic acid or its complement under low stringency conditions,

(ix) "Integral membrane transporter protein" (SEQ ID No:173) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane transporter protein" encoded by a nucleic acid that hybridizes to the "Integral membrane transporter protein" nucleic acid or its complement under low stringency conditions,

(x) "KIAA1949 (FRAGMENT)" (SEQ ID No:71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "KIAA1949 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or(xi)

"STX10" (SEQ ID No:150) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STX10" encoded by a nucleic acid that hybridizes to the "STX10" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

The invention further relates to the following embodiments of the Paladin-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "Paladin" (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "AOP2" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AOP2" encoded by a nucleic acid that hybridizes to the "AOP2" nucleic acid or its complement under low stringency conditions,

(ii) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,

(iii) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions,

(iv) "USP7" (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP7" encoded by a nucleic acid that hybridizes to the "USP7" nucleic acid or its complement under low stringency conditions, and

(v) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two



of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Paladin (SEQ ID NO. 179), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Paladin' encoded by a nucleic acid that hybridizes to the 'Paladin' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "AOP2" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AOP2" encoded by a nucleic acid that hybridizes to the "AOP2" nucleic acid or its complement under low stringency conditions,
- (ii) "Paladin" (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (iii) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,
- (iv) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions,

(v) "USP7" (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP7" encoded by a nucleic acid that hybridizes to the "USP7" nucleic acid or its complement under low stringency conditions, and/or

(vi) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 4 of the following proteins:

(i) "AOP2" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AOP2" encoded by a nucleic acid that hybridizes to the "AOP2" nucleic acid or its complement under low stringency conditions,

(ii) "Paladin" (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(iii) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,

(iv) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions,

(v) "USP7" (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP7" encoded by a nucleic acid that hybridizes to the "USP7" nucleic acid or its complement under low stringency conditions,

(vi) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Paladin complex obtainable by a process according to any of No. 9 - 11.
13. Protein of the Paladin complex selected from
- (i) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,
  - (ii) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions, and
  - (iii) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured

salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or

(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,

(ii) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions, and/or

(iii) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid

that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease; .

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,

(ii) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions, and/or

(iii) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing Paladin complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether  
(i) "AOP2" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AOP2" encoded by a nucleic acid that hybridizes to the "AOP2" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "Paladin" (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or



(iii) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions, and/or

(iv) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions, and/or

(v) "USP7" (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP7" encoded by a nucleic acid that hybridizes to the "USP7" nucleic acid or its complement under low stringency conditions, and/or

(vi) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether  
(i) "AOP2" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AOP2" encoded by a nucleic acid that hybridizes to the "AOP2" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "Paladin" (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a

nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions, and/or

(iv) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions, and/or

(v) "USP7" (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP7" encoded by a nucleic acid that hybridizes to the "USP7" nucleic acid or its complement under low stringency conditions, and/or

(vi) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and

Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "AOP2" (SEQ ID No:178) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AOP2" encoded by a nucleic acid that hybridizes to the "AOP2" nucleic acid or its complement under low stringency conditions,
- (ii) "Paladin" (SEQ ID No:179) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (iii) "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" (SEQ ID No:180) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" encoded by a nucleic acid that hybridizes to the "Similar to BCL2-associated athanogene 2 (Hypothetical protein)" nucleic acid or its complement under low stringency conditions,
- (iv) "TNRC6" (SEQ ID No:181) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC6" encoded by a

nucleic acid that hybridizes to the "TNRC6" nucleic acid or its complement under low stringency conditions,

(v) "USP7" (SEQ ID No:182) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP7" encoded by a nucleic acid that hybridizes to the "USP7" nucleic acid or its complement under low stringency conditions, and/or (vi) "flj11198, member of the abc transporter family" (SEQ ID No:183) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "flj11198, member of the abc transporter family" encoded by a nucleic acid that hybridizes to the "flj11198, member of the abc transporter family" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

The invention further relates to the following embodiments of the TFCP2-complex

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and
    - (ii) "TFCP2" (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TFCP2" encoded by a nucleic acid that hybridizes to the "TFCP2" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one second protein, which second protein is selected from the group consisting of:
    - (i) "LBP-9" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LBP-9" encoded by a nucleic acid that hybridizes to the "LBP-9" nucleic acid or its complement under low stringency conditions,

(ii) "RR42\_HUMAN" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RR42\_HUMAN" encoded by a nucleic acid that hybridizes to the "RR42\_HUMAN" nucleic acid or its complement under low stringency conditions,

(iii) "TF LBP-1b" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TF LBP-1b" encoded by a nucleic acid that hybridizes to the "TF LBP-1b" nucleic acid or its complement under low stringency conditions, and

(iv) "TRAP25" (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRAP25" encoded by a nucleic acid that hybridizes to the "TRAP25" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein TFCEP2 (SEQ ID NO. 187), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'TFCEP2' encoded by a nucleic acid that hybridizes to the 'TFCEP2' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (ii) "LBP-9" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LBP-9" encoded by a

nucleic acid that hybridizes to the "LBP-9" nucleic acid or its complement under low stringency conditions,

(iii) "RR42\_HUMAN" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RR42\_HUMAN" encoded by a nucleic acid that hybridizes to the "RR42\_HUMAN" nucleic acid or its complement under low stringency conditions,

(iv) "TF LBP-1b" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TF LBP-1b" encoded by a nucleic acid that hybridizes to the "TF LBP-1b" nucleic acid or its complement under low stringency conditions,

(v) "TFCP2" (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TFCP2" encoded by a nucleic acid that hybridizes to the "TFCP2" nucleic acid or its complement under low stringency conditions, and/or

(vi) "TRAP25" (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRAP25" encoded by a nucleic acid that hybridizes to the "TRAP25" nucleic acid or its complement under low stringency conditions,

and a protein complex selected from complex (II) and comprising the following proteins:

(i) "LBP-9" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LBP-9" encoded by a nucleic acid that hybridizes to the "LBP-9" nucleic acid or its complement under low stringency conditions,

(ii) "RR42\_HUMAN" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RR42\_HUMAN" encoded by a nucleic acid that hybridizes to the "RR42\_HUMAN" nucleic acid or its complement under low stringency conditions,

(iii) "TF LBP-1b" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TF LBP-1b" encoded by a nucleic acid that hybridizes to the "TF LBP-1b" nucleic acid or its complement under low stringency conditions,

(iv) "TFCP2" (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TFCP2" encoded by a

nucleic acid that hybridizes to the "TFCP2" nucleic acid or its complement under low stringency conditions, and/or

(v) "TRAP25" (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRAP25" encoded by a nucleic acid that hybridizes to the "TRAP25" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 3 of the following proteins:

(i) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(ii) "LBP-9" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LBP-9" encoded by a nucleic acid that hybridizes to the "LBP-9" nucleic acid or its complement under low stringency conditions,

(iii) "RR42\_HUMAN" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RR42\_HUMAN" encoded by a nucleic acid that hybridizes to the "RR42\_HUMAN" nucleic acid or its complement under low stringency conditions,

(iv) "TF LBP-1b" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TF LBP-1b" encoded by a nucleic acid that hybridizes to the "TF LBP-1b" nucleic acid or its complement under low stringency conditions,

(v) "TFCP2" (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TFCP2" encoded by a nucleic acid that hybridizes to the "TFCP2" nucleic acid or its complement under low stringency conditions,

(vi) "TRAP25" (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRAP25" encoded by a nucleic acid that hybridizes to the "TRAP25" nucleic acid or its complement under low stringency conditions.



5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the TFCP2 obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1(a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1(b).

14. Host cell containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. .

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8..

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease;.

23. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8. comprising the steps of

- (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

24. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing TFCEP2 to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

25. The method of No. 24, wherein the amount of said complex is determined.

26. The method of No. 24, wherein the activity of said complex is determined.

27. The method of No. 26, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

28. The method of No. 24, wherein the amount of the individual protein components of said complex are determined.

29. The method of No. 28, wherein said determining step comprises determining whether

- (i) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "LBP-9" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LBP-9" encoded by a nucleic acid that hybridizes to the "LBP-9" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "RR42\_HUMAN" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RR42\_HUMAN" encoded by a nucleic acid that hybridizes to the "RR42\_HUMAN" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "TF LBP-1b" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TF LBP-1b" encoded by a nucleic acid that hybridizes to the "TF LBP-1b" nucleic acid or its complement under low stringency conditions, and/or
- (v) "TFCP2" (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TFCP2" encoded by a nucleic acid that hybridizes to the "TFCP2" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "TRAP25" (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRAP25"

encoded by a nucleic acid that hybridizes to the "TRAP25" nucleic acid or its complement under low stringency conditions, is present in the complex.

30. The method of any of No. 24 - 29, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

31. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

32. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

33. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

34. The method of No. 33, wherein the amount of said complex is determined.

35. The method of No. 33, wherein the activity of said complex is determined.

36. The method of No. 35, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

37. The method of No. 33, wherein the amount of the individual protein components of said complex is determined.

38. The method of No. 37, wherein said determining step comprises determining whether

- (i) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "LBP-9" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LBP-9" encoded by a nucleic acid that hybridizes to the "LBP-9" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "RR42\_HUMAN" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RR42\_HUMAN" encoded by a nucleic acid that hybridizes to the "RR42\_HUMAN" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "TF LBP-1b" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TF LBP-1b" encoded by a nucleic acid that hybridizes to the "TF LBP-1b" nucleic acid or its complement under low stringency conditions, and/or
- (v) "TFCP2" (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TFCP2" encoded by a nucleic acid that hybridizes to the "TFCP2" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "TRAP25" (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRAP25"

encoded by a nucleic acid that hybridizes to the "TRAP25" nucleic acid or its complement under low stringency conditions, is present in the complex.

39. The complex of any one of No. 1 - 8 or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

40. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

41. The method according to No. 40, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

42. The method according to No. 40, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

43. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,  
(ii) "LBP-9" (SEQ ID No:184) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LBP-9" encoded by a nucleic acid that hybridizes to the "LBP-9" nucleic acid or its complement under low stringency conditions,  
(iii) "RR42\_HUMAN" (SEQ ID No:185) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"RR42\_HUMAN" encoded by a nucleic acid that hybridizes to the "RR42\_HUMAN" nucleic acid or its complement under low stringency conditions,

(iv) "TF LBP-1b" (SEQ ID No:186) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TF LBP-1b" encoded by a nucleic acid that hybridizes to the "TF LBP-1b" nucleic acid or its complement under low stringency conditions,

(v) "TFCP2" (SEQ ID No:187) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TFCP2" encoded by a nucleic acid that hybridizes to the "TFCP2" nucleic acid or its complement under low stringency conditions, and/or (vi) "TRAP25" (SEQ ID No:188) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRAP25" encoded by a nucleic acid that hybridizes to the "TRAP25" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;

The invention further relates to the following embodiments of the p75 NTR-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "NRAGE/MAGED1" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"NRAGE/MAGED1" encoded by a nucleic acid that hybridizes to the "NRAGE/MAGED1" nucleic acid or its complement under low stringency conditions,

(ii) "Nogo receptor" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo receptor" encoded by a nucleic acid that hybridizes to the "Nogo receptor" nucleic acid or its complement under low stringency conditions,

(iii) "Rho-GDI" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Rho-GDI" encoded by a nucleic acid that hybridizes to the "Rho-GDI" nucleic acid or its complement under low stringency conditions, and



- (iv) "p75 NTR" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "p75 NTR" encoded by a nucleic acid that hybridizes to the "p75 NTR" nucleic acid or its complement under low stringency conditions, and
- (b) at least one second protein, which second protein is selected from the group consisting of:
  - (i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
  - (ii) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the "DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions,
  - (iii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions,
  - (iv) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and
  - (v) "VAPA" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VAPA" encoded by a nucleic acid that hybridizes to the "VAPA" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl

(pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein p75 NTR (SEQ ID NO. 193), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'p75 NTR' encoded by a nucleic acid that hybridizes to the 'p75 NTR' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

(i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,

(ii) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the "DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions,

(iii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions,

(iv) "NRAGE/MAGED1" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRAGE/MAGED1" encoded by a nucleic acid that hybridizes to the "NRAGE/MAGED1" nucleic acid or its complement under low stringency conditions,

(v) "Nogo receptor" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo receptor" encoded by a nucleic acid that hybridizes to the "Nogo receptor" nucleic acid or its complement under low stringency conditions,

- (vi) "Rho-GDI" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Rho-GDI" encoded by a nucleic acid that hybridizes to the "Rho-GDI" nucleic acid or its complement under low stringency conditions,
- (vii) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,
- (viii) "VAPA" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VAPA" encoded by a nucleic acid that hybridizes to the "VAPA" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "p75 NTR" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "p75 NTR" encoded by a nucleic acid that hybridizes to the "p75 NTR" nucleic acid or its complement under low stringency conditions,
- and a protein complex selected from complex (II) and comprising the following proteins:
- (i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,
- (ii) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the "DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions,
- (iii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions,

(iv) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,

(v) "VAPA" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VAPA" encoded by a nucleic acid that hybridizes to the "VAPA" nucleic acid or its complement under low stringency conditions, and/or

(vi) "p75 NTR" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "p75 NTR" encoded by a nucleic acid that hybridizes to the "p75 NTR" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 4 of the following proteins:

(i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,

(ii) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the "DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions,

(iii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions,

(iv) "NRAGE/MAGED1" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"NRAGE/MAGED1" encoded by a nucleic acid that hybridizes to the "NRAGE/MAGED1" nucleic acid or its complement under low stringency conditions,

(v) "Nogo receptor" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo receptor" encoded by a nucleic acid that hybridizes to the "Nogo receptor" nucleic acid or its complement under low stringency conditions,

(vi) "Rho-GDI" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Rho-GDI" encoded by a nucleic acid that hybridizes to the "Rho-GDI" nucleic acid or its complement under low stringency conditions,

(vii) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,

(viii) "VAPA" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VAPA" encoded by a nucleic acid that hybridizes to the "VAPA" nucleic acid or its complement under low stringency conditions,

(ix) "p75 NTR" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "p75 NTR" encoded by a nucleic acid that hybridizes to the "p75 NTR" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the p75 NTR complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the p75 NTR complex selected from

- (i) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the "DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions, and
- (ii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of

proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.

18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.

19. The kit according to No. 18 for processing a substrate of said complex.

20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the



"DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions, and/or

(ii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease;.

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the "DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions, and/or

(ii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing p75 NTR complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether

- (i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the

"DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions, and/or

(iii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions, and/or

(iv) "NRAGE/MAGED1" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRAGE/MAGED1" encoded by a nucleic acid that hybridizes to the "NRAGE/MAGED1" nucleic acid or its complement under low stringency conditions, and/or

(v) "Nogo receptor" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo receptor" encoded by a nucleic acid that hybridizes to the "Nogo receptor" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Rho-GDI" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Rho-GDI" encoded by a nucleic acid that hybridizes to the "Rho-GDI" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and/or

(viii) "VAPA" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VAPA" encoded by a nucleic acid that hybridizes to the "VAPA" nucleic acid or its complement under low stringency conditions, and/or

(ix) "p75 NTR" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "p75 NTR" encoded by a nucleic acid that hybridizes to the "p75 NTR" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.
34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
36. The method of No. 35, wherein the amount of said complex is determined.
37. The method of No. 35, wherein the activity of said complex is determined.
38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said

complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether  
(i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the "DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions, and/or

(iii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions, and/or

(iv) "NRAGE/MAGED1" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRAGE/MAGED1" encoded by a nucleic acid that hybridizes to the "NRAGE/MAGED1" nucleic acid or its complement under low stringency conditions, and/or

(v) "Nogo receptor" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo receptor" encoded by a nucleic acid that hybridizes to the "Nogo receptor" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Rho-GDI" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Rho-GDI"

encoded by a nucleic acid that hybridizes to the "Rho-GDI" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions, and/or

(viii) "VAPA" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VAPA" encoded by a nucleic acid that hybridizes to the "VAPA" nucleic acid or its complement under low stringency conditions, and/or

(ix) "p75 NTR" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "p75 NTR" encoded by a nucleic acid that hybridizes to the "p75 NTR" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a

Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "Cadherin EGF LAG seven-pass G-type receptor 2" (SEQ ID No:157) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cadherin EGF LAG seven-pass G-type receptor 2" encoded by a nucleic acid that hybridizes to the "Cadherin EGF LAG seven-pass G-type receptor 2" nucleic acid or its complement under low stringency conditions,

(ii) "DKFZP586F1524 protein" (SEQ ID No:95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DKFZP586F1524 protein" encoded by a nucleic acid that hybridizes to the "DKFZP586F1524 protein" nucleic acid or its complement under low stringency conditions,

(iii) "HYPOTHETICAL PROTEIN FLJ39249" (SEQ ID No:162) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN FLJ39249" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN FLJ39249" nucleic acid or its complement under low stringency conditions,

(iv) "NRAGE/MAGED1" (SEQ ID No:189) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRAGE/MAGED1" encoded by a nucleic acid that hybridizes to the "NRAGE/MAGED1" nucleic acid or its complement under low stringency conditions,

(v) "Nogo receptor" (SEQ ID No:190) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nogo receptor" encoded by a nucleic acid that hybridizes to the "Nogo receptor" nucleic acid or its complement under low stringency conditions,

- (vi) "Rho-GDI" (SEQ ID No:191) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Rho-GDI" encoded by a nucleic acid that hybridizes to the "Rho-GDI" nucleic acid or its complement under low stringency conditions,
- (vii) "Thioredoxin domain-containing protein" (SEQ ID No:172) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Thioredoxin domain-containing protein" encoded by a nucleic acid that hybridizes to the "Thioredoxin domain-containing protein" nucleic acid or its complement under low stringency conditions,
- (viii) "VAPA" (SEQ ID No:192) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VAPA" encoded by a nucleic acid that hybridizes to the "VAPA" nucleic acid or its complement under low stringency conditions, and/or (ix) "p75 NTR" (SEQ ID No:193) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "p75 NTR" encoded by a nucleic acid that hybridizes to the "p75 NTR" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease;.

The invention further relates to the following embodiments of the Lamezin-complex

- 1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Lamezin/FKRP" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Lamezin/FKRP" encoded by a nucleic acid that hybridizes to the "Lamezin/FKRP" nucleic acid or its complement under low stringency conditions, and
    - (ii) "Presenilin1 " (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin1 " encoded by a nucleic acid that hybridizes to the "Presenilin1 " nucleic acid or its complement under low stringency conditions, and
  - (b) at least one second protein, which second protein is selected from the group consisting of:



- (i) "ASPH" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ASPH" encoded by a nucleic acid that hybridizes to the "ASPH" nucleic acid or its complement under low stringency conditions,
- (ii) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions,
- (iii) "CLNS1A" (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLNS1A" encoded by a nucleic acid that hybridizes to the "CLNS1A" nucleic acid or its complement under low stringency conditions,
- (iv) "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" encoded by a nucleic acid that hybridizes to the "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" nucleic acid or its complement under low stringency conditions,
- (v) "CNTNAP1" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNTNAP1" encoded by a nucleic acid that hybridizes to the "CNTNAP1" nucleic acid or its complement under low stringency conditions,
- (vi) "COX5B" (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX5B" encoded by a nucleic acid that hybridizes to the "COX5B" nucleic acid or its complement under low stringency conditions,
- (vii) "COX6B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6B" encoded by a nucleic acid that hybridizes to the "COX6B" nucleic acid or its complement under low stringency conditions,
- (viii) "COX6C" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6C"

encoded by a nucleic acid that hybridizes to the "COX6C" nucleic acid or its complement under low stringency conditions,

(ix) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions,

(x) "DICER1" (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DICER1" encoded by a nucleic acid that hybridizes to the "DICER1" nucleic acid or its complement under low stringency conditions,

(xi) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions,

(xii) "EC 6.3.2.19 (Fragment)" (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EC 6.3.2.19 (Fragment)" encoded by a nucleic acid that hybridizes to the "EC 6.3.2.19 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xiii) "EIF2B2" (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EIF2B2" encoded by a nucleic acid that hybridizes to the "EIF2B2" nucleic acid or its complement under low stringency conditions,

(xiv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(xv) "G2AN" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "G2AN" encoded by a nucleic acid that hybridizes to the "G2AN" nucleic acid or its complement under low stringency conditions,

(xvi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" encoded by a nucleic acid that hybridizes to the

"Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xvii) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions,

(xviii) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions,

(xix) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xx) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxi) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxii) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xxiii) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to

the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions,

(xxiv) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxv) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxvi) "IGF2R" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IGF2R" encoded by a nucleic acid that hybridizes to the "IGF2R" nucleic acid or its complement under low stringency conditions,

(xxvii) "ITGAV" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGAV" encoded by a nucleic acid that hybridizes to the "ITGAV" nucleic acid or its complement under low stringency conditions,

(xxviii) "ITPR2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR2" encoded by a nucleic acid that hybridizes to the "ITPR2" nucleic acid or its complement under low stringency conditions,

(xxix) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions,

(xxx) "LPHH1" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LPHH1" encoded by a nucleic acid that hybridizes to the "LPHH1" nucleic acid or its complement under low stringency conditions,

(xxxi) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xxxii) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions,

(xxxiii) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xxxiv) "Neural cell adhesion molecule L1 " (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neural cell adhesion molecule L1 " encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,

(xxxv) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxxvi) "Nuclear protein SDK3" (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nuclear protein SDK3" encoded by a nucleic acid that hybridizes to the "Nuclear protein SDK3" nucleic acid or its complement under low stringency conditions,

(xxxvii) "PPIB" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PPIB" encoded by a nucleic acid that hybridizes to the "PPIB" nucleic acid or its complement under low stringency conditions,

(xxxviii) "PTDSS1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTDSS1" encoded by a nucleic acid that hybridizes to the "PTDSS1" nucleic acid or its complement under low stringency conditions,

(xxxix) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xli) "SCG2" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SCG2" encoded by a nucleic acid that hybridizes to the "SCG2" nucleic acid or its complement under low stringency conditions,

(xlii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions,

(xlii) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions,

(xliii) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions,

(xliv) "TLOC1" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,

(xlv) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(xlvi) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin"

encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xlvii) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions,

(xlviii) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions,

(xlix) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions, and

(l) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions,

(li) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions,

and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Lamezin (SEQ ID NO. 222), or a functionally active derivative thereof, or a functionally active

fragment thereof, or a homolog thereof, or a variant of 'Lamezin' encoded by a nucleic acid that hybridizes to the 'Lamezin' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "ASPH" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ASPH" encoded by a nucleic acid that hybridizes to the "ASPH" nucleic acid or its complement under low stringency conditions,
- (ii) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions,
- (iii) "CLNS1A" (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLNS1A" encoded by a nucleic acid that hybridizes to the "CLNS1A" nucleic acid or its complement under low stringency conditions,
- (iv) "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" encoded by a nucleic acid that hybridizes to the "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" nucleic acid or its complement under low stringency conditions,
- (v) "CNTNAP1" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNTNAP1" encoded by a nucleic acid that hybridizes to the "CNTNAP1" nucleic acid or its complement under low stringency conditions,
- (vi) "COX5B" (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX5B" encoded by a nucleic acid that hybridizes to the "COX5B" nucleic acid or its complement under low stringency conditions,



- (vii) "COX6B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6B" encoded by a nucleic acid that hybridizes to the "COX6B" nucleic acid or its complement under low stringency conditions,
- (viii) "COX6C" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6C" encoded by a nucleic acid that hybridizes to the "COX6C" nucleic acid or its complement under low stringency conditions,
- (ix) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions,
- (x) "DICER1" (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DICER1" encoded by a nucleic acid that hybridizes to the "DICER1" nucleic acid or its complement under low stringency conditions,
- (xi) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions,
- (xii) "EC 6.3.2.19 (Fragment)" (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EC 6.3.2.19 (Fragment)" encoded by a nucleic acid that hybridizes to the "EC 6.3.2.19 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xiii) "EIF2B2" (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EIF2B2" encoded by a nucleic acid that hybridizes to the "EIF2B2" nucleic acid or its complement under low stringency conditions,
- (xiv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
- (xv) "G2AN" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "G2AN" encoded by a

nucleic acid that hybridizes to the "G2AN" nucleic acid or its complement under low stringency conditions,

(xvi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xvii) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions,

(xviii) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions,

(xix) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xx) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxi) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxii) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)"

encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xxiii) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions,

(xxiv) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxv) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxvi) "IGF2R" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IGF2R" encoded by a nucleic acid that hybridizes to the "IGF2R" nucleic acid or its complement under low stringency conditions,

(xxvii) "ITGAV" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGAV" encoded by a nucleic acid that hybridizes to the "ITGAV" nucleic acid or its complement under low stringency conditions,

(xxviii) "ITPR2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR2" encoded by a nucleic acid that hybridizes to the "ITPR2" nucleic acid or its complement under low stringency conditions,

(xxix) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the

"KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions,

(xxx) "LPHH1" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LPHH1" encoded by a nucleic acid that hybridizes to the "LPHH1" nucleic acid or its complement under low stringency conditions,

(xxxi) "Lamezin/FKRP" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Lamezin/FKRP" encoded by a nucleic acid that hybridizes to the "Lamezin/FKRP" nucleic acid or its complement under low stringency conditions,

(xxxii) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xxxiii) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions,

(xxxiv) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xxxv) "Neural cell adhesion molecule L1 " (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neural cell adhesion molecule L1 " encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,

(xxxvi) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxxvii) "Nuclear protein SDK3" (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"Nuclear protein SDK3" encoded by a nucleic acid that hybridizes to the "Nuclear protein SDK3" nucleic acid or its complement under low stringency conditions,

(xxxviii) "PPIB" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PPIB" encoded by a nucleic acid that hybridizes to the "PPIB" nucleic acid or its complement under low stringency conditions,

(xxxix) "PTDSS1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTDSS1" encoded by a nucleic acid that hybridizes to the "PTDSS1" nucleic acid or its complement under low stringency conditions,

(xl) "Presenilin1 " (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin1 " encoded by a nucleic acid that hybridizes to the "Presenilin1 " nucleic acid or its complement under low stringency conditions,

(xli) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xlii) "SCG2" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SCG2" encoded by a nucleic acid that hybridizes to the "SCG2" nucleic acid or its complement under low stringency conditions,

(xlili) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions,

(xliv) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions,

(xlv) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)"

encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions,

(xlvi) "TLOC1" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,

(xlvii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions,

(xlviii) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(xlix) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(l) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions,

(li) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions,

(lii) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions, and/or

- (liii) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, and a protein complex selected from complex (II) and comprising the following proteins:
- (i) "ASPH" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ASPH" encoded by a nucleic acid that hybridizes to the "ASPH" nucleic acid or its complement under low stringency conditions,
- (ii) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions,
- (iii) "CLNS1A" (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLNS1A" encoded by a nucleic acid that hybridizes to the "CLNS1A" nucleic acid or its complement under low stringency conditions,
- (iv) "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" encoded by a nucleic acid that hybridizes to the "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" nucleic acid or its complement under low stringency conditions,
- (v) "CNTNAP1" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNTNAP1" encoded by a nucleic acid that hybridizes to the "CNTNAP1" nucleic acid or its complement under low stringency conditions,
- (vi) "COX5B" (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX5B" encoded by a nucleic acid that hybridizes to the "COX5B" nucleic acid or its complement under low stringency conditions,

- (vii) "COX6B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6B" encoded by a nucleic acid that hybridizes to the "COX6B" nucleic acid or its complement under low stringency conditions,
- (viii) "COX6C" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6C" encoded by a nucleic acid that hybridizes to the "COX6C" nucleic acid or its complement under low stringency conditions,
- (ix) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions,
- (x) "DICER1" (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DICER1" encoded by a nucleic acid that hybridizes to the "DICER1" nucleic acid or its complement under low stringency conditions,
- (xi) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions,
- (xii) "EC 6.3.2.19 (Fragment)" (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EC 6.3.2.19 (Fragment)" encoded by a nucleic acid that hybridizes to the "EC 6.3.2.19 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xiii) "EIF2B2" (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EIF2B2" encoded by a nucleic acid that hybridizes to the "EIF2B2" nucleic acid or its complement under low stringency conditions,
- (xiv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
- (xv) "G2AN" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "G2AN" encoded by a



nucleic acid that hybridizes to the "G2AN" nucleic acid or its complement under low stringency conditions,

(xvi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xvii) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions,

(xviii) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions,

(xix) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xx) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxi) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxii) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)"

encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xxiii) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions,

(xxiv) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxv) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxvi) "IGF2R" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IGF2R" encoded by a nucleic acid that hybridizes to the "IGF2R" nucleic acid or its complement under low stringency conditions,

(xxvii) "ITGAV" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGAV" encoded by a nucleic acid that hybridizes to the "ITGAV" nucleic acid or its complement under low stringency conditions,

(xxviii) "ITPR2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR2" encoded by a nucleic acid that hybridizes to the "ITPR2" nucleic acid or its complement under low stringency conditions,

(xxix) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the

"KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions,

(xxx) "LPHH1" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LPHH1" encoded by a nucleic acid that hybridizes to the "LPHH1" nucleic acid or its complement under low stringency conditions,

(xxxi) "Lamezin/FKRP" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Lamezin/FKRP" encoded by a nucleic acid that hybridizes to the "Lamezin/FKRP" nucleic acid or its complement under low stringency conditions,

(xxxii) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xxxiii) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions,

(xxxiv) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xxxv) "Neural cell adhesion molecule L1 " (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neural cell adhesion molecule L1 " encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,

(xxxvi) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxxvii) "Nuclear protein SDK3" (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"Nuclear protein SDK3" encoded by a nucleic acid that hybridizes to the "Nuclear protein SDK3" nucleic acid or its complement under low stringency conditions,  
 (xxxviii) "PPIB" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PPIB" encoded by a nucleic acid that hybridizes to the "PPIB" nucleic acid or its complement under low stringency conditions,

(xxxix) "PTDSS1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTDSS1" encoded by a nucleic acid that hybridizes to the "PTDSS1" nucleic acid or its complement under low stringency conditions,

(xl) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xli) "SCG2" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SCG2" encoded by a nucleic acid that hybridizes to the "SCG2" nucleic acid or its complement under low stringency conditions,

(xlii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions,

(xlili) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions,

(xliv) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions,

(xlv) "TLOC1" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1"

encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,

(xlvi) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(xlvii) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xlviii) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions,

(xlix) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions,

(l) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions, and/or

(li) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 49 of the following proteins:

- (i) "ASPH" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ASPH" encoded by a nucleic acid that hybridizes to the "ASPH" nucleic acid or its complement under low stringency conditions,
- (ii) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions,
- (iii) "CLNS1A" (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLNS1A" encoded by a nucleic acid that hybridizes to the "CLNS1A" nucleic acid or its complement under low stringency conditions,
- (iv) "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" encoded by a nucleic acid that hybridizes to the "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" nucleic acid or its complement under low stringency conditions,
- (v) "CNTNAP1" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNTNAP1" encoded by a nucleic acid that hybridizes to the "CNTNAP1" nucleic acid or its complement under low stringency conditions,
- (vi) "COX5B" (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX5B" encoded by a nucleic acid that hybridizes to the "COX5B" nucleic acid or its complement under low stringency conditions,
- (vii) "COX6B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6B" encoded by a nucleic acid that hybridizes to the "COX6B" nucleic acid or its complement under low stringency conditions,
- (viii) "COX6C" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6C"

encoded by a nucleic acid that hybridizes to the "COX6C" nucleic acid or its complement under low stringency conditions,

(ix) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions,

(x) "DICER1" (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DICER1" encoded by a nucleic acid that hybridizes to the "DICER1" nucleic acid or its complement under low stringency conditions,

(xi) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions,

(xii) "EC 6.3.2.19 (Fragment)" (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EC 6.3.2.19 (Fragment)" encoded by a nucleic acid that hybridizes to the "EC 6.3.2.19 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xiii) "EIF2B2" (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EIF2B2" encoded by a nucleic acid that hybridizes to the "EIF2B2" nucleic acid or its complement under low stringency conditions,

(xiv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(xv) "G2AN" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "G2AN" encoded by a nucleic acid that hybridizes to the "G2AN" nucleic acid or its complement under low stringency conditions,

(xvi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" encoded by a nucleic acid that hybridizes to the

"Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xvii) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions,

(xviii) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions,

(xix) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xx) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxi) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxii) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xxiii) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to



the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions,

(xxiv) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxv) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxvi) "IGF2R" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IGF2R" encoded by a nucleic acid that hybridizes to the "IGF2R" nucleic acid or its complement under low stringency conditions,

(xxvii) "ITGAV" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGAV" encoded by a nucleic acid that hybridizes to the "ITGAV" nucleic acid or its complement under low stringency conditions,

(xxviii) "ITPR2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR2" encoded by a nucleic acid that hybridizes to the "ITPR2" nucleic acid or its complement under low stringency conditions,

(xxix) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions,

(xxx) "LPHH1" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LPHH1" encoded by a nucleic acid that hybridizes to the "LPHH1" nucleic acid or its complement under low stringency conditions,

- (xxxi) "Lamezin/FKRP" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Lamezin/FKRP" encoded by a nucleic acid that hybridizes to the "Lamezin/FKRP" nucleic acid or its complement under low stringency conditions,
- (xxxii) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,
- (xxxiii) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions,
- (xxxiv) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,
- (xxxv) "Neural cell adhesion molecule L1 " (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neural cell adhesion molecule L1 " encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,
- (xxxvi) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxxvii) "Nuclear protein SDK3" (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nuclear protein SDK3" encoded by a nucleic acid that hybridizes to the "Nuclear protein SDK3" nucleic acid or its complement under low stringency conditions,
- (xxxviii) "PPIB" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PPIB" encoded by a nucleic acid that hybridizes to the "PPIB" nucleic acid or its complement under low stringency conditions,

- (xxxix) "PTDSS1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTDSS1" encoded by a nucleic acid that hybridizes to the "PTDSS1" nucleic acid or its complement under low stringency conditions,
- (xl) "Presenilin1 " (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin1 " encoded by a nucleic acid that hybridizes to the "Presenilin1 " nucleic acid or its complement under low stringency conditions,
- (xli) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,
- (xlii) "SCG2" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SCG2" encoded by a nucleic acid that hybridizes to the "SCG2" nucleic acid or its complement under low stringency conditions,
- (xliii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions,
- (xliv) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions,
- (xlv) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xlvi) "TLOC1" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,

- (xlvii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions,
- (xlviii) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions,
- (xlix) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (l) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions,
- (li) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions,
- (lii) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions,
- (liii) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Lamezin complex obtainable by a process according to any of No. 9 - 11.
13. Protein of the Lamezin complex selected from
  - (i) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions,
  - (ii) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions,
  - (iii) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions,
  - (iv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
  - (v) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions,
  - (vi) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a

nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions,

(vii) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions,

(viii) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(ix) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(x) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xi) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions,

(xii) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xiii) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid

that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xiv) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions,

(xv) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions,

(xvi) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xvii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions,

(xviii) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions,

(xix) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions,

(xx) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the



"VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(xxi) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxii) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions,

(xxiii) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions,

(xxiv) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the

"ensp00000258417" nucleic acid or its complement under low stringency conditions, and

(xxv) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions,

wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or  
(b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.
18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
19. The kit according to No. 18 for processing a substrate of said complex.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as

Alzheimer's disease, congenital muscular dystrophy 1C and limb-girdle muscular dystrophy 2;.

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions,
- (ii) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions,
- (iii) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions,
- (iv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
- (v) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions,

- (vi) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions,
- (vii) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (viii) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,
- (ix) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,
- (x) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xi) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions,
- (xii) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions,

- (xiii) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions,
- (xv) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions,
- (xvi) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,
- (xvii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions,
- (xviii) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions,
- (xix) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions,

(xx) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(xxi) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxii) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions,

(xxiii) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions,

(xxiv) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease, congenital muscular dystrophy 1C and limb-girdle muscular dystrophy 2;

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

- (i) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions,
- (ii) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions,
- (iii) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions,
- (iv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
- (v) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions,
- (vi) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions,
- (vii) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions,

- (viii) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,
- (ix) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,
- (x) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,
- (xi) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions,
- (xii) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xiii) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the



"KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions,

(xv) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions,

(xvi) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xvii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions,

(xviii) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions,

(xix) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions,

(xx) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(xxi) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxii) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions,

(xxiii) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions,

(xxiv) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, comprising the steps of

(a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and

(b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing Lamezin complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity,

protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether

(i) "ASPH" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ASPH" encoded by a nucleic acid that hybridizes to the "ASPH" nucleic acid or its complement under low stringency conditions, and/or

(ii) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions, and/or

(iii) "CLNS1A" (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLNS1A" encoded by a nucleic acid that hybridizes to the "CLNS1A" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" (SEQ ID No:197) or a

- functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" encoded by a nucleic acid that hybridizes to the "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CNTNAP1" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNTNAP1" encoded by a nucleic acid that hybridizes to the "CNTNAP1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "COX5B" (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX5B" encoded by a nucleic acid that hybridizes to the "COX5B" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "COX6B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6B" encoded by a nucleic acid that hybridizes to the "COX6B" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "COX6C" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6C" encoded by a nucleic acid that hybridizes to the "COX6C" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions, and/or
- (x) "DICER1" (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DICER1" encoded by a nucleic acid that hybridizes to the "DICER1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions, and/or

- (xii) "EC 6.3.2.19 (Fragment)" (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EC 6.3.2.19 (Fragment)" encoded by a nucleic acid that hybridizes to the "EC 6.3.2.19 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "EIF2B2" (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EIF2B2" encoded by a nucleic acid that hybridizes to the "EIF2B2" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "G2AN" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "G2AN" encoded by a nucleic acid that hybridizes to the "G2AN" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329

(Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or

(xx) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "IGF2R" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IGF2R"

encoded by a nucleic acid that hybridizes to the "IGF2R" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "ITGAV" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGAV" encoded by a nucleic acid that hybridizes to the "ITGAV" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "ITPR2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR2" encoded by a nucleic acid that hybridizes to the "ITPR2" nucleic acid or its complement under low stringency conditions, and/or

(xxix) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions, and/or

(xxx) "LPHH1" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LPHH1" encoded by a nucleic acid that hybridizes to the "LPHH1" nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "Lamezin/FKRP" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Lamezin/FKRP" encoded by a nucleic acid that hybridizes to the "Lamezin/FKRP" nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442"

encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "Neural cell adhesion molecule L1 " (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neural cell adhesion molecule L1 " encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "Nuclear protein SDK3" (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nuclear protein SDK3" encoded by a nucleic acid that hybridizes to the "Nuclear protein SDK3" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "PPIB" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PPIB" encoded by a nucleic acid that hybridizes to the "PPIB" nucleic acid or its complement under low stringency conditions, and/or

(xxxix) "PTDSS1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTDSS1" encoded by a nucleic acid that hybridizes to the "PTDSS1" nucleic acid or its complement under low stringency conditions, and/or

(xl) "Presenilin1 " (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin1 " encoded by a nucleic acid that hybridizes to the "Presenilin1 " nucleic acid or its complement under low stringency conditions, and/or

(xli) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or

(xlii) "SCG2" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SCG2" encoded by a



nucleic acid that hybridizes to the "SCG2" nucleic acid or its complement under low stringency conditions, and/or

(xliii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions, and/or

(xliv) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions, and/or

(xlv) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions, and/or

(xlvi) "TLOC1" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions, and/or

(xlvii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions, and/or

(xlviii) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions, and/or

(xlix) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or

(i) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions, and/or

(iii) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions, and/or

(iiii) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease, congenital muscular dystrophy 1C and limb-girdle muscular dystrophy 2;.

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease, congenital muscular dystrophy 1C and limb-girdle muscular dystrophy 2;.

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity,

composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "ASPH" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ASPH" encoded by a

nucleic acid that hybridizes to the "ASPH" nucleic acid or its complement under low stringency conditions, and/or

(ii) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions, and/or

(iii) "CLNS1A" (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLNS1A" encoded by a nucleic acid that hybridizes to the "CLNS1A" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" encoded by a nucleic acid that hybridizes to the "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" nucleic acid or its complement under low stringency conditions, and/or

(v) "CNTNAP1" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNTNAP1" encoded by a nucleic acid that hybridizes to the "CNTNAP1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "COX5B" (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX5B" encoded by a nucleic acid that hybridizes to the "COX5B" nucleic acid or its complement under low stringency conditions, and/or

(vii) "COX6B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6B" encoded by a nucleic acid that hybridizes to the "COX6B" nucleic acid or its complement under low stringency conditions, and/or

(viii) "COX6C" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6C" encoded by a nucleic acid that hybridizes to the "COX6C" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "CSGlcA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSGlcA-T" encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions, and/or
- (x) "DICER1" (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DICER1" encoded by a nucleic acid that hybridizes to the "DICER1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "EC 6.3.2.19 (Fragment)" (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EC 6.3.2.19 (Fragment)" encoded by a nucleic acid that hybridizes to the "EC 6.3.2.19 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "EIF2B2" (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EIF2B2" encoded by a nucleic acid that hybridizes to the "EIF2B2" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "G2AN" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "G2AN" encoded by a nucleic acid that hybridizes to the "G2AN" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions, and/or

- (xvii) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions, and/or

- (xxiv) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "IGF2R" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IGF2R" encoded by a nucleic acid that hybridizes to the "IGF2R" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "ITGAV" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGAV" encoded by a nucleic acid that hybridizes to the "ITGAV" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "ITPR2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR2" encoded by a nucleic acid that hybridizes to the "ITPR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "LPFH1" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LPFH1" encoded by a nucleic acid that hybridizes to the "LPFH1" nucleic acid or its complement under low stringency conditions, and/or
- (xxxi) "Lamezin/FKRP" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"Lamezin/FKRP" encoded by a nucleic acid that hybridizes to the "Lamezin/FKRP" nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "Neural cell adhesion molecule L1 " (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neural cell adhesion molecule L1 " encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "Nuclear protein SDK3" (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nuclear protein SDK3" encoded by a nucleic acid that hybridizes to the "Nuclear protein SDK3" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "PPIB" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PPIB" encoded by a nucleic acid that hybridizes to the "PPIB" nucleic acid or its complement under low stringency conditions, and/or

(xxxix) "PTDSS1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTDSS1"



encoded by a nucleic acid that hybridizes to the "PTDSS1" nucleic acid or its complement under low stringency conditions, and/or

(xl) "Presenilin1 " (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin1 " encoded by a nucleic acid that hybridizes to the "Presenilin1 " nucleic acid or its complement under low stringency conditions, and/or

(xli) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or

(xlii) "SCG2" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SCG2" encoded by a nucleic acid that hybridizes to the "SCG2" nucleic acid or its complement under low stringency conditions, and/or

(xliii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions, and/or

(xliv) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions, and/or

(xlv) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions, and/or

(xlvi) "TLOC1" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions, and/or

(xlvii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2"

encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions, and/or

(xlviii) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions, and/or

(xlix) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or

(l) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions, and/or

(li) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions, and/or

(lii) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions, and/or

(liii) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease, congenital muscular dystrophy 1C and limb-girdle muscular dystrophy 2;

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
 (i) "ASPH" (SEQ ID No:194) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ASPH" encoded by a nucleic acid that hybridizes to the "ASPH" nucleic acid or its complement under low stringency conditions,

- (ii) "C7orf14" (SEQ ID No:195) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C7orf14" encoded by a nucleic acid that hybridizes to the "C7orf14" nucleic acid or its complement under low stringency conditions,
- (iii) "CLNS1A" (SEQ ID No:196) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLNS1A" encoded by a nucleic acid that hybridizes to the "CLNS1A" nucleic acid or its complement under low stringency conditions,
- (iv) "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" (SEQ ID No:197) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" encoded by a nucleic acid that hybridizes to the "CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)" nucleic acid or its complement under low stringency conditions,
- (v) "CNTNAP1" (SEQ ID No:198) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNTNAP1" encoded by a nucleic acid that hybridizes to the "CNTNAP1" nucleic acid or its complement under low stringency conditions,
- (vi) "COX5B" (SEQ ID No:199) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX5B" encoded by a nucleic acid that hybridizes to the "COX5B" nucleic acid or its complement under low stringency conditions,
- (vii) "COX6B" (SEQ ID No:200) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6B" encoded by a nucleic acid that hybridizes to the "COX6B" nucleic acid or its complement under low stringency conditions,
- (viii) "COX6C" (SEQ ID No:201) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COX6C" encoded by a nucleic acid that hybridizes to the "COX6C" nucleic acid or its complement under low stringency conditions,
- (ix) "CSG1cA-T" (SEQ ID No:86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CSG1cA-T"

encoded by a nucleic acid that hybridizes to the "CSGlcA-T" nucleic acid or its complement under low stringency conditions,

(x) "DICER1" (SEQ ID No:202) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DICER1" encoded by a nucleic acid that hybridizes to the "DICER1" nucleic acid or its complement under low stringency conditions,

(xi) "DREV1" (SEQ ID No:203) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DREV1" encoded by a nucleic acid that hybridizes to the "DREV1" nucleic acid or its complement under low stringency conditions,

(xii) "EC 6.3.2.19 (Fragment)" (SEQ ID No:204) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EC 6.3.2.19 (Fragment)" encoded by a nucleic acid that hybridizes to the "EC 6.3.2.19 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xiii) "EIF2B2" (SEQ ID No:205) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EIF2B2" encoded by a nucleic acid that hybridizes to the "EIF2B2" nucleic acid or its complement under low stringency conditions,

(xiv) "EXTL2" (SEQ ID No:206) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(xv) "G2AN" (SEQ ID No:207) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "G2AN" encoded by a nucleic acid that hybridizes to the "G2AN" nucleic acid or its complement under low stringency conditions,

(xvi) "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" (SEQ ID No:208) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" encoded by a nucleic acid that hybridizes to the "Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3" nucleic acid or its complement under low stringency conditions,

(xvii) "HIV-1 Vpr-binding protein (Fragment)" (SEQ ID No:209) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a

variant of "HIV-1 Vpr-binding protein (Fragment)" encoded by a nucleic acid that hybridizes to the "HIV-1 Vpr-binding protein (Fragment)" nucleic acid or its complement under low stringency conditions,

(xviii) "HPIP" (SEQ ID No:210) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HPIP" encoded by a nucleic acid that hybridizes to the "HPIP" nucleic acid or its complement under low stringency conditions,

(xix) "HSPC329 (Fragment)" (SEQ ID No:211) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSPC329 (Fragment)" encoded by a nucleic acid that hybridizes to the "HSPC329 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xx) "HYPOTHETICAL PROTEIN" (SEQ ID No:212) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxi) "HYPOTHETICAL PROTEIN" (SEQ ID No:213) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN" nucleic acid or its complement under low stringency conditions,

(xxii) "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" (SEQ ID No:214) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" encoded by a nucleic acid that hybridizes to the "HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT)" nucleic acid or its complement under low stringency conditions,

(xxiii) "Hypothetical protein FLJ34763" (SEQ ID No:215) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein FLJ34763" encoded by a nucleic acid that hybridizes to the "Hypothetical protein FLJ34763" nucleic acid or its complement under low stringency conditions,

(xxiv) "Hypothetical protein KIAA0062 (Fragment)" (SEQ ID No:216) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA0062 (Fragment)" encoded by a nucleic acid

that hybridizes to the "Hypothetical protein KIAA0062 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxv) "Hypothetical protein KIAA1500 (Fragment)" (SEQ ID No:217) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Hypothetical protein KIAA1500 (Fragment)" encoded by a nucleic acid that hybridizes to the "Hypothetical protein KIAA1500 (Fragment)" nucleic acid or its complement under low stringency conditions,

(xxvi) "IGF2R" (SEQ ID No:218) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IGF2R" encoded by a nucleic acid that hybridizes to the "IGF2R" nucleic acid or its complement under low stringency conditions,

(xxvii) "ITGAV" (SEQ ID No:219) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITGAV" encoded by a nucleic acid that hybridizes to the "ITGAV" nucleic acid or its complement under low stringency conditions,

(xxviii) "ITPR2" (SEQ ID No:220) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR2" encoded by a nucleic acid that hybridizes to the "ITPR2" nucleic acid or its complement under low stringency conditions,

(xxix) "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" (SEQ ID No:164) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" encoded by a nucleic acid that hybridizes to the "KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa" nucleic acid or its complement under low stringency conditions,

(xxx) "LPHH1" (SEQ ID No:221) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LPHH1" encoded by a nucleic acid that hybridizes to the "LPHH1" nucleic acid or its complement under low stringency conditions,

(xxxi) "Lamezin/FKRP" (SEQ ID No:222) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Lamezin/FKRP" encoded by a nucleic acid that hybridizes to the "Lamezin/FKRP" nucleic acid or its complement under low stringency conditions,

(xxxii) "Laminin, gamma 1 " (SEQ ID No:88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Laminin, gamma 1 " encoded by a nucleic acid that hybridizes to the "Laminin, gamma 1 " nucleic acid or its complement under low stringency conditions,

(xxxiii) "MAGEB4" (SEQ ID No:223) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MAGEB4" encoded by a nucleic acid that hybridizes to the "MAGEB4" nucleic acid or its complement under low stringency conditions,

(xxxiv) "MGC5442" (SEQ ID No:224) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MGC5442" encoded by a nucleic acid that hybridizes to the "MGC5442" nucleic acid or its complement under low stringency conditions,

(xxxv) "Neural cell adhesion molecule L1 " (SEQ ID No:225) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neural cell adhesion molecule L1 " encoded by a nucleic acid that hybridizes to the "Neural cell adhesion molecule L1 " nucleic acid or its complement under low stringency conditions,

(xxxvi) "Neurotrypsin" (SEQ ID No:91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxxvii) "Nuclear protein SDK3" (SEQ ID No:226) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nuclear protein SDK3" encoded by a nucleic acid that hybridizes to the "Nuclear protein SDK3" nucleic acid or its complement under low stringency conditions,

(xxxviii) "PPIB" (SEQ ID No:227) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PPIB" encoded by a nucleic acid that hybridizes to the "PPIB" nucleic acid or its complement under low stringency conditions,

(xxxix) "PTDSS1" (SEQ ID No:228) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTDSS1" encoded by a nucleic acid that hybridizes to the "PTDSS1" nucleic acid or its complement under low stringency conditions,



- (xl) "Presenilin1 " (SEQ ID No:123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Presenilin1 " encoded by a nucleic acid that hybridizes to the "Presenilin1 " nucleic acid or its complement under low stringency conditions,
- (xli) "Reelin" (SEQ ID No:97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,
- (xlii) "SCG2" (SEQ ID No:229) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SCG2" encoded by a nucleic acid that hybridizes to the "SCG2" nucleic acid or its complement under low stringency conditions,
- (xliii) "SIMILAR TO HYPOTHETICAL PROTEIN SB153" (SEQ ID No:230) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SIMILAR TO HYPOTHETICAL PROTEIN SB153" encoded by a nucleic acid that hybridizes to the "SIMILAR TO HYPOTHETICAL PROTEIN SB153" nucleic acid or its complement under low stringency conditions,
- (xliv) "STRA6 isoform 1" (SEQ ID No:231) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STRA6 isoform 1" encoded by a nucleic acid that hybridizes to the "STRA6 isoform 1" nucleic acid or its complement under low stringency conditions,
- (xlv) "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" (SEQ ID No:232) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" encoded by a nucleic acid that hybridizes to the "Similar to RIKEN cDNA 1100001L14 gene (Fragment)" nucleic acid or its complement under low stringency conditions,
- (xlvi) "TLOC1" (SEQ ID No:233) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,
- (xlvii) "UGCGL2" (SEQ ID No:102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL2" encoded by a nucleic acid that hybridizes to the "UGCGL2" nucleic acid or its complement under low stringency conditions,

(xlviii) "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" (SEQ ID No:234) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" encoded by a nucleic acid that hybridizes to the "VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR" nucleic acid or its complement under low stringency conditions,

(xlix) "Wolframin" (SEQ ID No:235) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(l) "bzw1: basic leucine zipper and w2 domains 1" (SEQ ID No:236) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "bzw1: basic leucine zipper and w2 domains 1" encoded by a nucleic acid that hybridizes to the "bzw1: basic leucine zipper and w2 domains 1" nucleic acid or its complement under low stringency conditions,

(li) "dkfzp586c1924" (SEQ ID No:237) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "dkfzp586c1924" encoded by a nucleic acid that hybridizes to the "dkfzp586c1924" nucleic acid or its complement under low stringency conditions,

(lii) "ensp00000258417" (SEQ ID No:238) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ensp00000258417" encoded by a nucleic acid that hybridizes to the "ensp00000258417" nucleic acid or its complement under low stringency conditions,

and/or (liii) "hyou1: hypoxia up-regulated 1" (SEQ ID No:103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "hyou1: hypoxia up-regulated 1" encoded by a nucleic acid that hybridizes to the "hyou1: hypoxia up-regulated 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease, congenital muscular dystrophy 1C and limb-girdle muscular dystrophy 2;.

The present invention further relates to the following embodiments of the APP-C59-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "C59" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C59" encoded by a nucleic acid that hybridizes to the "C59" nucleic acid or its complement under low stringency conditions,

(ii) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65L1" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(iv) "TIP60" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and

(v) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

(i) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(ii) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a

nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions,

(iii) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions,

(iv) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III" encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions,

(v) "GTF3C3" (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GTF3C3" encoded by a nucleic acid that hybridizes to the "GTF3C3" nucleic acid or its complement under low stringency conditions,

(vi) "NRD1" (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRD1" encoded by a nucleic acid that hybridizes to the "NRD1" nucleic acid or its complement under low stringency conditions,

(vii) "S100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100 beta" encoded by a nucleic acid that hybridizes to the "S100 beta" nucleic acid or its complement under low stringency conditions, and

(viii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein C59 (SEQ ID NO. 239), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'C59' encoded by a nucleic acid that hybridizes to the 'C59' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

(i) "C59" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C59" encoded by a nucleic acid that hybridizes to the "C59" nucleic acid or its complement under low stringency conditions,

(ii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(iii) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions,

(iv) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions,

(v) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III" encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions,

(vi) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(vii) "Fe65L1" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1"

encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(viii) "GTF3C3" (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GTF3C3" encoded by a nucleic acid that hybridizes to the "GTF3C3" nucleic acid or its complement under low stringency conditions,

(ix) "NRD1" (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRD1" encoded by a nucleic acid that hybridizes to the "NRD1" nucleic acid or its complement under low stringency conditions,

(x) "S100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100 beta" encoded by a nucleic acid that hybridizes to the "S100 beta" nucleic acid or its complement under low stringency conditions,

(xi) "TIP60" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(xii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1 - 7 of the following proteins:

(i) "C59" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C59" encoded by a nucleic acid that hybridizes to the "C59" nucleic acid or its complement under low stringency conditions,

- (ii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (iii) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions,
- (iv) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions,
- (v) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III" encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions,
- (vi) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (vii) "Fe65L1" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (viii) "GTF3C3" (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GTF3C3" encoded by a nucleic acid that hybridizes to the "GTF3C3" nucleic acid or its complement under low stringency conditions,
- (ix) "NRD1" (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRD1" encoded by a nucleic acid that hybridizes to the "NRD1" nucleic acid or its complement under low stringency conditions,
- (x) "S100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100 beta"

encoded by a nucleic acid that hybridizes to the "S100 beta" nucleic acid or its complement under low stringency conditions,

(xi) "TIP60" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(xii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions,

(xiii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).



9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the APP-C59/AICD complex obtainable by a process according to any of No. 9 - 11.

13. Protein of the APP-C59/AICD complex selected from

(i) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions, and

(ii) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III" encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

14. Nucleic acid encoding a protein according to No. 13.

15. Construct, preferably a vector construct, comprising (a) a nucleic acid according to No. 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
- (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
16. Host cell, containing a vector comprising at least one of the nucleic acid of No. 14 and/or a construct of No. 15 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. 13.
18. A kit comprising in one or more container the complex of any of No. 1 - 8 and/or the proteins of No. 13 optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
19. The kit according to No. 18 for processing a substrate of said complex.
20. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

21. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one protein according to No. 14 and/or at least one antibody according to No. 17 is attached to a solid carrier.

22. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

23. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III" encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

24. A pharmaceutical composition according to No. 23 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease; .

25. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8 and/or any of the following the proteins:

(i) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III"

encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions, comprising the steps of

- (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing APP-C59/AICD complex to one or more candidate molecules; and

- (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

27. The method of No. 26, wherein the amount of said complex is determined.

28. The method of No. 26, wherein the activity of said complex is determined.

29. The method of No. 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

30. The method of No. 26, wherein the amount of the individual protein components of said complex are determined.

31. The method of No. 30, wherein said determining step comprises determining whether (i) "C59" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C59" encoded by a nucleic acid that hybridizes to the "C59" nucleic acid or its complement under low stringency conditions, and/or

(ii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or

(iii) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions, and/or

(v) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III" encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Fe65L1" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "GTF3C3" (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GTF3C3"

encoded by a nucleic acid that hybridizes to the "GTF3C3" nucleic acid or its complement under low stringency conditions, and/or

(ix) "NRD1" (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRD1" encoded by a nucleic acid that hybridizes to the "NRD1" nucleic acid or its complement under low stringency conditions, and/or

(x) "S100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100 beta" encoded by a nucleic acid that hybridizes to the "S100 beta" nucleic acid or its complement under low stringency conditions, and/or

(xi) "TIP60" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or

(xii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

32. The method of any of No. 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

34. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity,

composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

36. The method of No. 35, wherein the amount of said complex is determined.

37. The method of No. 35, wherein the activity of said complex is determined.

38. The method of No. 37, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

39. The method of No. 35, wherein the amount of the individual protein components of said complex is determined.

40. The method of No. 39, wherein said determining step comprises determining whether (i) "C59" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C59" encoded by a nucleic

acid that hybridizes to the "C59" nucleic acid or its complement under low stringency conditions, and/or

(ii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or

(iii) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions, and/or

(v) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III" encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Fe65L1" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "GTF3C3" (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GTF3C3" encoded by a nucleic acid that hybridizes to the "GTF3C3" nucleic acid or its complement under low stringency conditions, and/or

(ix) "NRD1" (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRD1" encoded by a nucleic acid that hybridizes to the "NRD1" nucleic acid or its complement under low stringency conditions, and/or



- (x) "S100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100 beta" encoded by a nucleic acid that hybridizes to the "S100 beta" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "TIP60" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

41. The complex of any one of No. 1 - 8, or proteins of No. 13 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

43. The method according to No. 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

44. The method according to No. 42 , wherein said disease or disorder involves increased levels of the amount or activity of said complex.

45. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "C59" (SEQ ID No:239) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C59" encoded by a nucleic acid that hybridizes to the "C59" nucleic acid or its complement under low stringency conditions,

(ii) "COPS3" (SEQ ID No:47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(iii) "CPNE7" (SEQ ID No:240) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPNE7" encoded by a nucleic acid that hybridizes to the "CPNE7" nucleic acid or its complement under low stringency conditions,

(iv) "CUL3" (SEQ ID No:51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CUL3" encoded by a nucleic acid that hybridizes to the "CUL3" nucleic acid or its complement under low stringency conditions,

(v) "Copine III" (SEQ ID No:241) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Copine III" encoded by a nucleic acid that hybridizes to the "Copine III" nucleic acid or its complement under low stringency conditions,

(vi) "Fe65" (SEQ ID No:135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(vii) "Fe65L1" (SEQ ID No:242) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(viii) "GTF3C3" (SEQ ID No:243) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GTF3C3"

encoded by a nucleic acid that hybridizes to the "GTF3C3" nucleic acid or its complement under low stringency conditions,

(ix) "NRD1" (SEQ ID No:244) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NRD1" encoded by a nucleic acid that hybridizes to the "NRD1" nucleic acid or its complement under low stringency conditions,

(x) "S100 beta" (SEQ ID No:26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100 beta" encoded by a nucleic acid that hybridizes to the "S100 beta" nucleic acid or its complement under low stringency conditions,

(xi) "TIP60" (SEQ ID No:245) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(xii) "USP11" (SEQ ID No:66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "USP11" encoded by a nucleic acid that hybridizes to the "USP11" nucleic acid or its complement under low stringency conditions, and/or (xiii) "X11beta" (SEQ ID No:74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease; .

The invention further relates to the following embodiments of the BRI-complex

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane protein 2B (ITM2B)" encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions, and

(b) at least one second protein, which second protein is selected from the group consisting of:

- (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "CARBOXYPEPTIDASE D" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CARBOXYPEPTIDASE D" encoded by a nucleic acid that hybridizes to the "CARBOXYPEPTIDASE D" nucleic acid or its complement under low stringency conditions,
- (iv) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (v) "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" encoded by a nucleic acid that hybridizes to the "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" nucleic acid or its complement under low stringency conditions, and
- (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions, and
- (vii) "ITM2C" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions

and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein ITM2B (SEQ ID NO. 249), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'ITM2B' encoded by a nucleic acid that hybridizes to the 'ITM2B' under low stringency conditions.

3. The protein complex according to No. 1 selected from complex (I) and comprising the following proteins:

- (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "CARBOXYPEPTIDASE D" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CARBOXYPEPTIDASE D" encoded by a nucleic acid that hybridizes to the "CARBOXYPEPTIDASE D" nucleic acid or its complement under low stringency conditions,
- (iv) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,

(v) "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" encoded by a nucleic acid that hybridizes to the "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" nucleic acid or its complement under low stringency conditions,

(vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,

(vii) "ITM2C" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane protein 2B (ITM2B)" encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions,

and a protein complex selected from complex (II) and comprising the following proteins:

(i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "CARBOXYPEPTIDASE D" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CARBOXYPEPTIDASE D" encoded by a nucleic acid that hybridizes to the "CARBOXYPEPTIDASE D" nucleic acid or its complement under low stringency conditions,

- (iv) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
  - (v) "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" encoded by a nucleic acid that hybridizes to the "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" nucleic acid or its complement under low stringency conditions,
  - (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions, and/or
  - (vii) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane protein 2B (ITM2B)" encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions,
- and a protein complex selected from complex (III) and comprising the following proteins:
- (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof,
  - (ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof,
  - (iii) "CARBOXYPEPTIDASE D" (SEQ ID No:246) or a functionally active derivative thereof,
  - (iv) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof,
  - (v) "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" (SEQ ID No:247) or a functionally active derivative thereof,
  - (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof,
  - (vii) "ITM2C" (SEQ ID No:248) or a functionally active derivative thereof, and
  - (viii) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:249) or a functionally active derivative thereof,

4. The protein complex according to No. 1 comprising all but 1 - 5 of the following proteins:

- (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "CARBOXYPEPTIDASE D" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CARBOXYPEPTIDASE D" encoded by a nucleic acid that hybridizes to the "CARBOXYPEPTIDASE D" nucleic acid or its complement under low stringency conditions,
- (iv) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (v) "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" encoded by a nucleic acid that hybridizes to the "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" nucleic acid or its complement under low stringency conditions,
- (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,
- (vii) "ITM2C" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (viii) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane protein 2B (ITM2B)" encoded by a nucleic acid that



hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is

attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the BRI/ITM2B complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1(a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1(b).

14. Host cell containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody which binds to any of the proteins according to No. .

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and familial British dementia; .
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8..
22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease and familial British dementia; .
23. A method for screening for a molecule that binds to the complex of anyone of No. 1 - 8. comprising the steps of
  - (a) exposing said complex, or a cell or organism containing same to one or more candidate molecules; and
  - (b) determinig whether said candidate molecule is bound to the complex or protein.
24. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of (a) exposing said complex, or a cell or organism containing BRI/ITM2B complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

25. The method of No. 24, wherein the amount of said complex is determined.

26. The method of No. 24, wherein the activity of said complex is determined.

27. The method of No. 26, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

28. The method of No. 24, wherein the amount of the individual protein components of said complex are determined.

29. The method of No. 28, wherein said determining step comprises determining whether  
(i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

- (iii) "CARBOXYPEPTIDASE D" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CARBOXYPEPTIDASE D" encoded by a nucleic acid that hybridizes to the "CARBOXYPEPTIDASE D" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" encoded by a nucleic acid that hybridizes to the "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "ITM2C" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane protein 2B (ITM2B)" encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions, is present in the complex.

30. The method of any of No. 24 - 29, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and familial British dementia; .

31. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and familial British dementia; .
32. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
33. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
34. The method of No. 33, wherein the amount of said complex is determined.
35. The method of No. 33, wherein the activity of said complex is determined.
36. The method of No. 35, wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

37. The method of No. 33, wherein the amount of the individual protein components of said complex is determined.

38. The method of No. 37, wherein said determining step comprises determining whether  
(i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "CARBOXYPEPTIDASE D" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CARBOXYPEPTIDASE D" encoded by a nucleic acid that hybridizes to the "CARBOXYPEPTIDASE D" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions, and/or

(v) "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" encoded by a nucleic acid that hybridizes to the "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions, and/or

(vii) "ITM2C" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a

nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(viii) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane protein 2B (ITM2B)" encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions, is present in the complex.

39. The complex of any one of No. 1 - 8 or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and familial British dementia; .

40. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

41. The method according to No. 40, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.



42. The method according to No. 40 , wherein said disease or disorder involves increased levels of the amount or activity of said complex.

43. Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "APLP2" (SEQ ID No:4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No:5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "CARBOXYPEPTIDASE D" (SEQ ID No:246) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CARBOXYPEPTIDASE D" encoded by a nucleic acid that hybridizes to the "CARBOXYPEPTIDASE D" nucleic acid or its complement under low stringency conditions,
- (iv) "Contactin1" (SEQ ID No:12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Contactin1" encoded by a nucleic acid that hybridizes to the "Contactin1" nucleic acid or its complement under low stringency conditions,
- (v) "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" (SEQ ID No:247) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" encoded by a nucleic acid that hybridizes to the "DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)" nucleic acid or its complement under low stringency conditions,
- (vi) "Delta-like homolog" (SEQ ID No:160) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Delta-like homolog" encoded by a nucleic acid that hybridizes to the "Delta-like homolog" nucleic acid or its complement under low stringency conditions,
- (vii) "ITM2C" (SEQ ID No:248) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low

stringency conditions, and/or(viii) "Integral membrane protein 2B (ITM2B)" (SEQ ID No:249) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Integral membrane protein 2B (ITM2B)" encoded by a nucleic acid that hybridizes to the "Integral membrane protein 2B (ITM2B)" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and familial British dementia; .

## 5. PROTOCOLS:

The TAP-technology, which is more fully described in EP 1 105 508 B1 and in Rigaut, et al., 1999, Nature Biotechnol. 17:1030-1032 respectively was used and further adapted as described below for protein purification. Proteins were identified using mass spectrometry as described further below.

### 5.1 Construction of TAP-tagged bait

The cDNAs encoding the complete ORF were obtained by RT-PCR. Total RNA was prepared from appropriate cell lines using the RNeasy Mini Kit (Qiagen). Both cDNA synthesis and PCR were performed with the SUPERSCRIPT One-Step RT-PCR for Long templates Kit (Life Technologies) using gene-specific primers. After 35-40 cycles of amplification PCR-products with the expected size were gel-purified with the MinElute PCR Purification Kit (Qiagen) and, if necessary, used for further amplification. Low-abundant RNAs were amplified by nested PCR before gel-purification. Restriction sites for NotI were attached to PCR primers to allow subcloning of amplified cDNAs into the retroviral vectors pIE94-N/C-TAP thereby generating N- or C-terminal fusions with the TAP-tag (Rigaut et al., 1999, Nature Biotechnol. 17:1030-1032).

N-terminal tagging was chosen for the following baits/entry points: APP-C59, Dab1, PC7, TFCP2, Jip1.

C-terminal tagging was chosen for the following baits/entry points: Bace1, BRI, Fe65L2, Neurotrypsin, Telencephalin, .

Both N- and C-terminal tagging was used for the following baits/entry points: Bace2, p75-NTR, Hunc18a, Lamezin, Pilt, VTRP

Clones were analyzed by restriction digest, DNA sequencing and by in vitro translation using the TNT T7 Quick Coupled Transcription/Translation System (Promega inc.). The presence of the proteins was proven by Western blotting using the protein A part of the TAP-tag for detection. Briefly, separation of proteins by standard SDS-PAGE was followed by semi-dry transfer onto a nitrocellulose membrane (PROTRAN, Schleicher&Schuell) using the MultiphorII blotting apparatus from Pharmacia Biotech. The transfer buffer consisted of 48 mM Tris, 39 mM glycine, 10% methanol and 0,0375% sodium dodecylsulfate. After blocking in phosphate-buffered saline (PBS) supplemented with 10% dry milk powder and 0,1% Tween 20 transferred proteins were probed with the Peroxidase-Anti-Peroxidase Soluble Complex (Sigma) diluted in blocking solution. After intensive washing immunoreactive proteins were visualized by enhanced chemiluminescence (ECL; Amersham Pharmacia Biotech).

## 5.2 Preparation of Virus and infection

As a vector, a MoMLV-based recombinant virus was used.

The preparation has been carried out as follows:

### 5.2.1 Preparation of Virus

293 gp cells were grown to 100% confluency. They were split 1:5 on poly-L-Lysine plates (1:5 diluted poly-L-Lysine [0.01% stock solution, Sigma P-4832] in PBS, left on plates for at least 10 min.). On Day 2, 63 microgram of retroviral Vector DNA together with 13 microgram of DNA of plasmid encoding an appropriate envelope protein were transfected into 293 gp cells (Somia, et al., 1999, Proc. Natl. Acad. Sci. USA 96:12667-12672; Somia, et al. 2000, J. Virol. 74:4420-4424). On Day 3, the medium was replaced with 15 ml DMEM + 10% FBS per 15-cm dish. On Day 4, the medium containing viruses (supernatant) was harvested (at 24 h following medium change after transfection). When a second collection was planned, DMEM 10 % FBS was added to the plates and the plates were incubated for another 24 h. All collections were done as follows: The

supernatant was filtered through 0.45 micrometer filter (Corning GmbH, cellulose acetate, 431155). The filter was placed into konical polyallomer centrifuge tubes (Beckman, 358126) that are placed in buckets of a SW 28 rotor (Beckman). The filtered supernatant was ultracentrifuged at 19400 rpm in the SW 28 rotor, for 2 hours at 21 degree Celsius. The supernatant was discarded. The pellet containing viruses was resuspended in a small volume (for example 300 microliter) of Hank's Balanced Salt Solution [Gibco BRL, 14025-092], by pipetting up and down 100-times, using an aerosol-safe tip. The viruses were used for transfection as described below.

### 5.2.2 Infection

Cells that were infected were plated one day before into one well of a 6-well plate. 4 hours before infection, the old medium on the cells was replaced with fresh medium. Only a minimal volume was added, so that the cells are completely covered (e.g. 700 microliter). During infection, the cells were actively dividing.

A description of the cells and their growth conditions is given in 5.2.3

To the concentrated virus, polybrene (Hexadimethrine Bromide; Sigma, H 9268) was added to achieve a final concentration of 8 microgram/ml (this is equivalent to 2.4 microliter of the 1 milligram/ml polybrene stock per 300 microliter of concentrated retrovirus). The virus was incubated in polybrene at room temperature for 1 hour. For infection, the virus/polybrene mixture was added to the cells and incubated at 37 degree Celsius at the appropriate CO<sub>2</sub> concentration for several hours (e.g. over-day or over-night). Following infection, the medium on the infected cells was replaced with fresh medium. The cells were passaged as usual after they became confluent. The cells contain the retrovirus integrated into their chromosomes and stably express the gene of interest.

### 5.2.3 Cell lines

The following cell lines were used:

APP-C59-complex: SKN-BE2-cell line; Bace1-complex: SKN-BE2-cell line, HEK-293-cell line, Lan5-cell line; Bace2-complex: SKN-BE2-cell line; BRI-complex: SKN-BE2-cell line; mDab1-complex: SKN-BE2-cell line; Fe65L2-complex: SKN-BE2-cell line; P75-NTR-complex: SKN-BE2-cell line, HEK-293-cell line; Pilt-complex: SKN-BE2-cell line; Paladin-complex: SKN-BE2-cell line, HEK-293-cell line; Neurotrypsin-complex: SKN-BE2-cell line, HEK-293-cell line; Hunc18a-complex: SKN-BE2-cell line, Lan1-cell line; PC7-complex: SKN-BE2-cell line; TFCP2-complex: SKN-BE2-cell line; JIP1-complex: SKN-BE2-cell line, HEK-293-cell line; Lamezin-complex: SKN-BE2-cell line; VTRP-complex: SKN-BE2-cell line

For expression, SKN-BE2 cells were used. SKN-BE2 cells (American Type Culture Collection-No. CRL-2271) were grown in 95% OptiMEM + 5% iron-supplemented calf serum.

LAN-cells (human neuroblastoma cells) were grown in 90% RPMI 1640 + 10% FBS

The expression pattern of the TAP-tagged proteins was checked by immunoblot-analysis as described in 5.3.3 and/or by immunofluorescence as described in 5.3.1 or 5.3.2.

### 5.3 Checking of expression pattern of TAP-tagged proteins

The expression pattern of the TAP-tagged protein was checked by immunoblot analysis and/or by immunofluorescence. Immunofluorescence analysis was either carried out according to section 5.3.1 or to section 5.3.2 depending on the type of the TAP-tagged protein. Immunoblot analysis was carried out according to section 5.3.3.

#### 5.3.1 Protocol for the indirect Immunofluorescence staining of fixed mammalian cells for plasma membrane and ER bound proteins

Cells were grown in FCS media on polylysine coated 8 well chamber slides to 50% confluency. Then fixation of the cells was performed in 4% ParaFormAldehyde diluted in Phosphate Buffer Saline (PBS) solution (0.14M Phosphate, 0.1M NaCl pH 7.4). The cells were incubated for 30 minutes at room temperature in 300 microliters per well.

Quenching was performed in 0.1M Glycine in PBS for 2x 20 minutes at room temperature. Blocking was performed with 1% Bovine Serum Albumin (BSA) in 0.3% Saponin + PBS for at least 1 hour at room temperature. Incubation of the primary antibodies was performed in the blocking solution overnight at +4°C. The proper dilution of the antibodies was determined in a case to case basis. Cells were washed in PBS containing 0.3% Saponin for 2x 20 minutes at room temperature. Incubation of the secondary antibodies is performed in the blocking solution. Alexa 594 coupled goat anti-rabbit is diluted 1:1000 (Molecular Probes). Alexa 488 coupled goat anti-mouse is diluted 1:1000 (Molecular Probes). DAPI was used to label DNA. If Phalloidin was used to label F-actin, the drug is diluted 1:500 and incubated with the secondary antibodies. Cells were then washed again 2x 20 minutes at room temperature in PBS. The excess of buffer was removed and cells were mounted in a media containing an anti-bleaching agent (Vectashield, Vector Laboratories).

### 5.3.2 Protocol for the indirect Immunofluorescence staining of fixed mammalian cells for non-plasma membrane bound proteins:

Cells were grown in FCS media on Polylysine coated 8 well chamber slides to 50% confluency. Fixation of the cells was performed in 4% ParaFormaldehyde diluted in Phosphate Buffer Saline (PBS) solution (0.14M Phosphate, 0.1M NaCl pH 7.4) for 30 minutes at Room Temperature (RT), 300 microliters per well. Quenching was performed in 0.1M Glycine in PBS for 2x 20 minutes at room temperature. Permeabilization of cells was done with 0.5% Triton X-100 in PBS for 10 minutes at room temperature. Blocking was then done in 1% Bovine Serum Albumin (BSA) in 0.3% Saponin + PBS for at least 1 hour at RT (Blocking solution). Incubation of the primary antibodies was performed in the blocking solution, overnight at +4°C. The proper dilution of the antibodies has to be determined in a case to case basis. Cells were washed in PBS containing 0.3% Saponin, for 2x 20 minutes at RT. Incubation of the secondary antibodies was performed in the blocking solution. Alexa 594 coupled goat anti-rabbit is diluted 1:1000 (Molecular Probes), Alexa 488 coupled goat anti-mouse is diluted 1:1000 (Molecular Probes). DAPI was used to label DNA. If Phalloidin is used to label F-actin, the drug is diluted 1:500 and incubated with the secondary antibodies. Cells were washed 2x 20 minutes at RT in

PBS. The excess of buffer was removed and cells were mounted in a media containing an anti-bleaching agent (Vectashield, Vector Laboratories).

### 5.3.3 Immunoblot analysis

To analyze expression levels of TAP-tagged proteins, a cell pellet (from a 6-well dish) was lysed in 60  $\mu$ l DNase I buffer (5% Glycerol, 100 mM NaCl, 0.8 % NP-40 (IGEPAL), 5 mM magnesium sulfate, 100  $\mu$ g/ml DNase I (Roche Diagnostics), 50 mM Tris, pH 7.5, protease inhibitor cocktail) for 15 min on ice. Each sample was split into two aliquots. The first half was centrifuged at 13,000 rpm for 5 min. to yield the NP-40-extractable material in the supernatant; the second half (total material) was carefully triturated. 50  $\mu$ g each of the NP-40-extractable material and the total material are mixed with DTT-containing sample buffer for 30 min at 50°C on a shaker and separated by SDS polyacrylamide gel electrophoresis on a precast 4-12% Bis-Tris gel (Invitrogen). Proteins were then transferred to nitrocellulose using a semi-dry procedure with a discontinuous buffer system. Briefly, gel and nitrocellulose membrane were stacked between filter papers soaked in either anode buffer (three layers buffer A1 (0.3 M Tris-HCl) and three layers buffer A2 (0.03 M Tris-HCl)) or cathode buffer (three layers of 0.03 M Tris-HCl, pH 9.4, 0.1 % SDS, 40 mM  $\epsilon$ -aminocaproic acid). Electrotransfer of two gels at once was performed at 600 mA for 25 min. Transferred proteins were visualized with Ponceau S solution for one min to control transfer efficiency and then destained in water. The membrane was blocked in 5% non-fat milk powder in TBST (TBS containing 0.05% Tween-20) for 30 min at room temperature. It was subsequently incubated with HRP-coupled PAP antibody (1:5000 diluted in 5% milk/TBST) for 1 h at room temperature, washed three times for 10 min in TBST. The blot membrane was finally soaked in chemiluminescent substrate (ECL, Roche Diagnostics) for 2 min. and either exposed to X-ray film or analyzed on an imaging station.

### 5.4 Purification of protein complexes

Protein complex purification was adapted to the sub-cellular localization of the TAP-tagged protein and was performed as described below.

#### 5.4.1 Lysate preparation for cytoplasmic proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of CZ lysis buffer (50 mM Tris-Cl, pH 7.4; 5 % Glycerol; 0,2 % IGEPAL; 1.5 mM  $\text{MgCl}_2$ ; 100 mM NaCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was incubated for 30 min on ice and spun for 10 min at 20,000g. The supernatant was subjected to an additional ultracentrifugation step for 1 h at 100,000g. The supernatant was recovered and rapidly frozen in liquid nitrogen or immediately processed further.

#### 5.4.2 Lysate preparation for membrane proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of Membrane-Lysis buffer (50 mM Tris, pH 7.4; 7.5 % Glycerol; 1 mM EDTA; 150 mM NaCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was spun for 10 min at 750g, the supernatant was recovered and subjected to an ultracentrifugation step for 1 h at 100,000g. The membrane pellet was resuspended in 7,5 ml of Membrane-Lysis buffer containing 0.8% n-Dodecyl- $\beta$ -D-maltoside and incubated for 1 h at 4°C with constant agitation. The sample was subjected to another ultracentrifugation step for 1h at 100,000g and the solubilized material was quickly frozen in liquid nitrogen or immediately processed further.

#### 5.4.3 Lysate preparation for nuclear proteins



About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of Hypotonic-Lysis buffer (10 mM Tris, pH 7.4; 1.5 mM  $\text{MgCl}_2$ ; 10 mM KCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was spun for 10 min at 2,000g and the resulting supernatant (S1) saved on ice. The nuclear pellet (P1) was resuspended in 5 ml Nuclear-Lysis buffer (50 mM Tris, pH 7.4; 1.5 mM  $\text{MgCl}_2$ ; 20 % Glycerol; 420 mM NaCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and incubated for 30 min on ice. The sample was combined with S1, further diluted with 7 ml of Dilution buffer (110 mM Tris, pH 7.4; 0.7 % NP40; 1.5 mM  $\text{MgCl}_2$ ; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT), incubated on ice for 10 min and centrifuged at 100,000g for 1h. The final supernatant (S2) was frozen quickly in liquid nitrogen.

#### 5.4.4 Tandem Affinity Purification

The frozen lysate was quickly thawed in a 37°C water bath, and spun for 20 min at 100,000g. The supernatant was recovered and incubated with 0.2 ml of settled rabbit IgG-Agarose beads (Sigma) for 2 h with constant agitation at 4°C. Immobilized protein complexes were washed with 10 ml of CZ lysis buffer (containing 1 Complete™ tablet (Roche) per 50 ml of buffer) and further washed with 5 ml of TEV cleavage buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 0.5 mM EDTA; 1 mM DTT). Protein-complexes were eluted by incubation with 5  $\mu\text{l}$  of TEV protease (GibcoBRL, Cat.No. 10127-017) for 1 h at 16°C in 150  $\mu\text{l}$  TEV cleavage buffer. The eluate was recovered and combined with 0.2 ml settled Calmodulin affinity beads (Stratagene) in 0.2 ml CBP binding buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 2mM MgAc; 2mM Imidazole; 1mM DTT; 4 mM  $\text{CaCl}_2$ ) followed by 1 h incubation at 4°C with constant agitation. Immobilized protein complexes were washed with 10 ml of CBP wash buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 1mM MgAc; 1mM Imidazole; 1mM DTT; 2 mM  $\text{CaCl}_2$ ) and eluted by addition of 600  $\mu\text{l}$  CBP elution buffer (10 mM Tris, pH

8.0; 5 mM EGTA) for 5 min at 37°C. The eluate was recovered in a siliconized tube and lyophilized. The remaining Calmodulin resin was boiled for 5 min in 50  $\mu$ l 4x Laemmli sample buffer. The sample buffer was isolated, combined with the lyophilised fraction and loaded on a NuPAGE gradient gel (Invitrogen, 4-12%, 1.5 mm, 10 well).

#### 5.4.5 Isolation of the Sambiasin complex of the invention from mouse tissue

Two mouse forebrains (0.6314 g total wet weight) were lysed in 14 mls of 50 mM HEPES pH 7.4; 150 mM NaCl; 1 mM EDTA; 0.5 mM Sodium Vanadate; 10% Glycerol; 1% n-Dodecyl- $\beta$ -D-maltoside containing standard proteinase inhibitors. The tissue was homogenised in a Warring blender for 30 seconds on ice. Homogenates were incubated on ice for 1 hour and then centrifuged at 13,000 g for 30 min at 4°C. The resulting pellet was stored at -80°C while the supernatant was centrifuged at 50,000 g for 30 min at 4°C and the resulting pellet was also stored at -80°C. 6.5 ml of the supernatant from this second centrifugation step was taken and combined with 25  $\mu$ l of anti presenilin-1 antisera (MAB5232, Chemicon). The antibody/lysate mixture was incubated for 1 hour at 4°C with end-over end mixing. Pre-washed protein G sepharose was added and the mixture was incubated overnight at 4°C with end-over mixing. The protein G was recovered by centrifugation at 200 g for 5 min at 4°C. The protein G beads were then washed 5 times in 1ml lysis buffer (containing 0.1% n-Dodecyl- $\beta$ -D-maltoside rather than 1%). 100  $\mu$ l of NuPAGE sample buffer (Invitrogen) was added and the sample incubated at 37°C for 10 min. Samples were separated on 4-12 % NuPAGE bis/tris gels (Invitrogen, 1.5 mm, 10 well). Proteins were visualized by staining with colloidal coomassie (Sigma) and then analysed by LC/MSMS.

### 5.5 Protein identification by mass spectrometry

#### 5.5.1 Protein digestion prior to mass spectrometric analysis

Gel-separated proteins were reduced, alkylated and digested in gel essentially following the procedure described by Shevchenko et al., 1996, Anal. Chem. 68:850-858. Briefly, gel-separated proteins were excised from the gel using a clean scalpel, reduced

using 10 mM DTT (in 5mM ammonium bicarbonate, 54°C, 45 min) and subsequently alkylated with 55 mM iodoacetamid (in 5 mM ammonium bicarbonate) at room temperature in the dark (30 min). Reduced and alkylated proteins were digested in gel with porcine trypsin (Promega) at a protease concentration of 12.5 ng/ $\mu$ l in 5mM ammonium bicarbonate. Digestion was allowed to proceed for 4 hours at 37°C and the reaction was subsequently stopped using 5  $\mu$ l 5% formic acid.

### 5.5.2 Sample preparation prior to analysis by mass spectrometry

Gel plugs were extracted twice with 20  $\mu$ l 1% TFA and pooled with acidified digest supernatants. Samples were dried in a vacuum centrifuge and resuspended in 13  $\mu$ l 1% TFA.

### 5.5.3 Mass spectrometric data acquisition

Peptide samples were injected into a nano LC system (CapLC, Waters or Ultimate, Dionex) which was directly coupled either to a quadrupole TOF (QTOF2, QTOF Ultima, QTOF Micro, Micromass or QSTAR Pulsar, Sciex) or ion trap (LCQ Deca XP) mass spectrometer. Peptides were separated on the LC system using a gradient of aqueous and organic solvents (see below). Solvent A was 5% acetonitrile in 0.5% formic acid and solvent B was 70% acetonitrile in 0.5% formic acid.

Time (min)	% solvent A	% solvent B
0	95	5
5.33	92	8
35	50	50
36	20	80
40	20	80
41	95	5
50	95	5

Peptides eluting off the LC system were partially sequenced within the mass spectrometer.

#### 5.5.4 Protein identification

The peptide mass and fragmentation data generated in the LC-MS/MS experiments were used to query fasta formatted protein and nucleotide sequence databases maintained and updated regularly at the NCBI (for the NCBI nr, dbEST and the human and mouse genomes) and European Bioinformatics Institute (EBI, for the human, mouse, *D. melanogaster* and *C. elegans* proteome databases). Proteins were identified by correlating the measured peptide mass and fragmentation data with the same data computed from the entries in the database using the software tool Mascot (Matrix Science; Perkins et al., 1999, *Electrophoresis* 20:3551-3567). Search criteria varied depending on which mass spectrometer was used for the analysis.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

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TABLE 1

## COMPONENTS OF COMPLEXES

Name of complex	Entry Point	All interactors of the complex	Known interactors of the complex	Novel interactors of the complex	Proteins of unknown function
mDAB1-complex	mDAB1	ACE		ACE	
		APG-1		APG-1	
		APLP1	APLP1		
		APLP2	APLP2		
		ApoE receptor 2	ApoE receptor 2		
		APP	APP		
		Archvillin		Archvillin	
		Contactin1		Contactin1	
		CRK		CRK	
		CRKL		CRKL	
		CSNK1D		CSNK1D	
		CSNK1E		CSNK1E	
		DAB1	DAB1		
		DAB2IP		DAB2IP	
		DNAJB1		DNAJB1	DNAJB1

	hypothetical protein FLJ11151		hypothetical protein FLJ11151	hypothetical protein FLJ11151
	Hypothetical protein FLJ31432		Hypothetical protein FLJ31432	Hypothetical protein FLJ31432
	ISL1		ISL1	
	ITGA1		ITGA1	
	ITGB1		ITGB1	
	LDLR		LDLR	
	MAPK8IP3/JIP3		MAPK8IP3/JIP3	
	NEDD5		NEDD5	
	PLK		PLK	
	Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1		Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1	
	QPRT		QPRT	
	S-100 beta		S-100 beta	
	SIM TO PLEXIN 1 - MOUSE.		SIM TO PLEXIN 1 - MOUSE.	
	TGM5		TGM5	
	VLDL receptor	VLDL receptor		

JIP1-complex	JIP1	ALPHA-CENTRACTIN.		ALPHA-CENTRACTIN.	
		APP	APP		
		CASPASE-14 PRECURSOR.		CASPASE-14 PRECURSOR.	
		DCTN1		DCTN1	
		Dynactin 3, isoform 2		Dynactin 3, isoform 2	
		HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN.		HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN.	HARP11, UNCHARACTERIZE D HYPOTHALAMUS PROTEIN.
		ISLET-BRAIN 2.	ISLET-BRAIN 2.		
		JIP-1	JIP-1		
		JNK	JNK		
		Kif5c		Kif5c	
		KINESIN HC		KINESIN HC	
		KINESIN LC1.		KINESIN LC1.	
		MAPK8IP3/JIP3		MAPK8IP3/JIP3	
Fe65L2-complex	Fe65L2	APLP1	APLP1		
		APLP2	APLP2		

	APP	APP	
	CDC42BPB		CDC42BPB
	Contactin1		Contactin1
	COP9		COP9
	COP9 COMPLEX SUBUNIT 4.		COP9 COMPLEX SUBUNIT 4.
	COP9 complex subunit 7a		COP9 complex subunit 7a
	COPS3		COPS3
	COPS5		COPS5
	COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)		COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)
	COPS7B		COPS7B
	CUL3		CUL3
	Fe65L2	Fe65L2	
	FLJ12599		FLJ12599
	GPR49		GPR49
	GPS1		GPS1
	KIAA1102 PROTEIN (FRAGMENT).		KIAA1102 PROTEIN (FRAGMENT).
	NEDD8		NEDD8
			KIAA1102 PROTEIN (FRAGMENT).

		Protocadherin gamma C3		Protocadherin gamma C3	Protocadherin gamma C3
		RBX1		RBX1	
		RHOBTB1		RHOBTB1	RHOBTB1
		RHOBTB2		RHOBTB2	RHOBTB2
		SIM TO CGI-20		SIM TO CGI-20	SIM TO CGI-20
		SIMILAR TO POLYPROTEIN.		SIMILAR TO POLYPROTEIN.	SIMILAR TO POLYPROTEIN.
		TRIP15		TRIP15	
		TUBGCP3		TUBGCP3	
		USP11		USP11	USP11
Pit/TJP4-complex	Pit/TJP4	DLG1	DLG1	DLG1	DLG1
		HYPOTHETICAL PROTEIN (FRAGMENT).		HYPOTHETICAL PROTEIN (FRAGMENT).	HYPOTHETICAL PROTEIN (FRAGMENT).
		HYPOTHETICAL PROTEIN FLJ12599.		HYPOTHETICAL PROTEIN FLJ12599.	HYPOTHETICAL PROTEIN FLJ12599.
		HYPOTHETICAL PROTEIN FLJ35393.		HYPOTHETICAL PROTEIN FLJ35393.	HYPOTHETICAL PROTEIN FLJ35393.
		KIAA1102 (Fragment)		KIAA1102 (Fragment)	KIAA1102

						(Fragment)
		KIAA1949 (FRAGMENT)			KIAA1949 (FRAGMENT)	KIAA1949 (FRAGMENT)
		Pilt	Pilt			
		STMN3			STMN3	
		X11beta			X11beta	
Neurotrypsi n-complex	Neurotrypsin	ADAMTS1			ADAMTS1	
		ADAMTS19			ADAMTS19	ADAMTS19
		ADAMTS7			ADAMTS7	ADAMTS7
		CHRNA5			CHRNA5	
		CRTAP			CRTAP	CRTAP
		CU70_HUMAN			CU70_HUMAN	CU70_HUMAN
		DECR1			DECR1	
		DNAJC3			DNAJC3	
		ERP70			ERP70	
		GBTS1			GBTS1	GBTS1
		GRCB			GRCB	GRCB
		hyou1: hypoxia up-regulated 1			hyou1: hypoxia up-regulated 1	hyou1: hypoxia up-regulated 1

	Hypothetical protein KIAA1402 (Fragment)		Hypothetical protein KIAA1402 (Fragment)	Hypothetical protein KIAA1402 (Fragment)
	LAMB1		LAMB1	
	Laminin, gamma 1		Laminin, gamma 1	
	MT-ACT48		MT-ACT48	MT-ACT48
	Neurotrypsin	Neurotrypsin		
	NOTCH4-like protein (Hypothetical protein)		NOTCH4-like protein (Hypothetical protein)	
	PCDH16		PCDH16	PCDH16
	PLOD		PLOD	
	PLOD3		PLOD3	
	PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT.		PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT.	PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT.
	q8wvi0		q8wvi0	q8wvi0
	RAB39, MEMBER RAS ONCOGENE FAMILY.		RAB39, MEMBER RAS ONCOGENE FAMILY.	RAB39, MEMBER RAS ONCOGENE FAMILY.
	Reelin		Reelin	

	SC65		SC65	SC65
	Similar to hydroxysteroid 17-beta dehydrogenase 11		Similar to hydroxysteroid 17-beta dehydrogenase 11	Similar to hydroxysteroid 17-beta dehydrogenase 11
	Similar to hypothetical protein FLJ22329		Similar to hypothetical protein FLJ22329	Similar to hypothetical protein FLJ22329
	Similar to RIKEN cDNA 1300010F03 gene		Similar to RIKEN cDNA 1300010F03 gene	Similar to RIKEN cDNA 1300010F03 gene
	UGCGL2		UGCGL2	
Hunc18a-complex	Hunc18a ELAVL1		ELAVL1	
	Epim	Epim		
	FIGF		FIGF	
	Filamin, gamma		Filamin, gamma	
	GOLGA3		GOLGA3	GOLGA3
	Hunc18a	Hunc18a		
	hypothetical protein BC013764		hypothetical protein BC013764	hypothetical protein BC013764
	PAWR		PAWR	



		STX1A	STX1A			
		STX1B2	STX1B2			
		STX3A	STX3A			
		X11alpha	X11alpha			
		X11beta	X11beta			
Telencepha	Telencephali	APOD		APOD		
lin-complex	n					
		CALD1		CALD1		
		CALR		CALR		
		CD11a/CD18	CD11a/CD18 INTEGRIN,			
		INTEGRIN, BETA-2	BETA-2			
		CHRNA5		CHRNA5		
		HYPOTHETICAL		HYPOTHETICAL		
		PROTEIN FLJ35393.		PROTEIN FLJ35393.		HYPOTHETICAL
		OPA1		OPA1		PROTEIN FLJ35393.
		Presenilin 1	Presenilin 1			
		PYCS		PYCS		
		RAB6A		RAB6A		
		RAP1, GTP-GDP		RAP1, GTP-GDP		
		dissociation stimulator 1		dissociation stimulator 1		

		Telencephalin	Telencephalin	
PC7-complex	PC7	15 KDA SELENO- PROTEIN PRECURSOR.	15 KDA SELENO- PROTEIN PRECURSOR.	
		APP-C99	APP-C99	
		BACE1	BACE1	
		DNAJC3	DNAJC3	DNAJC3
		Neurotrypsin	Neurotrypsin	
		PC7	PC7	
		Protocadherin beta 7	Protocadherin beta 7	Protocadherin beta 7
VTRP-complex		PTPN1	PTPN1	
	VTRP	27 KDA GOLGI SNARE PROTEIN.	27 KDA GOLGI SNARE PROTEIN.	
		ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN.	ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN.	
		AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1.	AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1.	

	BCL2/ADENOVIRUS E1B 19KD- INTERACTING PROTEIN 1, ISOFORM BNIP1.		BCL2/ADENOVIRUS E1B 19KD- INTERACTING PROTEIN 1, ISOFORM BNIP1.	
	BET1	BET1		
	CALPAIN SMALL SUBUNIT.		CALPAIN SMALL SUBUNIT.	
	CENTROMERE/KINETO CHORE PROTEIN ZW10 HOMOLOG.		CENTROMERE/KINET OCHORE PROTEIN ZW10 HOMOLOG.	
	DYNACTIN COMPLEX 50 KDA SUBUNIT.		DYNACTIN COMPLEX 50 KDA SUBUNIT.	
	GP25L2 PROTEIN.		GP25L2 PROTEIN.	
	HSPC009.		HSPC009.	HSPC009.
	HYPOTH 61.5 KDA PROTEIN (FRAGMENT).		HYPOTH 61.5 KDA PROTEIN (FRAGMENT).	HYPOTH 61.5 KDA PROTEIN (FRAGMENT).
	HYPOTH 78.2 KDA PROTEIN (FRAGMENT).		HYPOTH 78.2 KDA PROTEIN (FRAGMENT).	HYPOTH 78.2 KDA PROTEIN (FRAGMENT).

	MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN.		MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN.	MDS032, UNCHARACTERIZE D HEMATOPOIETIC STEM/PROGENITO R CELLS PROTEIN.
	NEUROBLASTOMA- AMPLIFIED PROTEIN.		NEUROBLASTOMA- AMPLIFIED PROTEIN.	NEUROBLASTOMA- AMPLIFIED PROTEIN.
	Phosphatidylserine receptor		Phosphatidylserine receptor	
	RAD50-INTERACTING PROTEIN 1.		RAD50-INTERACTING PROTEIN 1.	
	SEC22B VESICLE TRAFFICKING PROTEIN		SEC22B VESICLE TRAFFICKING PROTEIN	
	Similar to golgi SNAP receptor complex member 1		Similar to golgi SNAP receptor complex member 1	
	SYNTAXIN 10.		SYNTAXIN 10.	
	SYNTAXIN 18.	SYNTAXIN 18.		
	SYNTAXIN 5.	SYNTAXIN 5.		

		VESICULAR-FUSION PROTEIN NSF.		VESICULAR-FUSION PROTEIN NSF.	
		VTRP		VTRP	
BACE1 (new)- complex	BACE1 (new)	BACE1		BACE1	
		Cadherin EGF LAG seven-pass G-type receptor 2		Cadherin EGF LAG seven-pass G-type receptor 2	Cadherin EGF LAG seven-pass G-type receptor 2
		Calsynenin 1		Calsynenin 1	
		CGI-13		CGI-13	
		Delta-6 fatty acid desaturase		Delta-6 fatty acid desaturase	
		Delta-like homolog		Delta-like homolog	
		FLJ30668		FLJ30668	FLJ30668
		FLJ39249		FLJ39249	FLJ39249
		integral membrane transporter protein		integral membrane transporter protein	
		ITCH		ITCH	
		KIAA1250		KIAA1250	KIAA1250
		kinectin 1 (kinesin receptor)		kinectin 1 (kinesin receptor)	

	Nicastrin	Nicastrin		
	Nogo-A		Nogo-A	
	PDGFRB		PDGFRB	
	PTK7		PTK7	
	SERPINA1		SERPINA1	
	SIM TO Y71H10A. 2.P.		SIM TO Y71H10A. 2.P.	SIM TO Y71H10A. 2.P.
	Sortilin-related receptor		Sortilin-related receptor	
	STX10		STX10	
	Thioredoxin domain-containing protein		Thioredoxin domain-containing protein	Thioredoxin domain-containing protein
BACE2-complex	APLP2		APLP2	
	BACE2	BACE2		
	Cadherin EGF LAG seven-pass G-type receptor 2		Cadherin EGF LAG seven-pass G-type receptor 2	
	Calsyntenin 1		Calsyntenin 1	
	Delta-like homolog		Delta-like homolog	
	FLJ10474		FLJ10474	FLJ10474
	FLJ14787		FLJ14787	FLJ14787

	Integral membrane transporter protein		Integral membrane transporter protein	
	ITCH		ITCH	
	KIAA1949 (FRAGMENT)		KIAA1949 (FRAGMENT)	KIAA1949 (FRAGMENT)
	STX10		STX10	
PALADIN-complex	AOP2		AOP2	
	fij11198, member of the abc transporter family		fij11198, member of the abc transporter family	fij11198, member of the abc transporter family
	Paladin	Paladin		
	Similar to BCL2-associated athanogene 2 (Hypothetical protein)		Similar to BCL2-associated athanogene 2 (Hypothetical protein)	Similar to BCL2-associated athanogene 2 (Hypothetical protein)
	TNRC6		TNRC6	TNRC6
	USP7		USP7	
TFCP2-complex	Fe65	Fe65		
	LBP-9		LBP-9	
	RR42_HUMAN		RR42_HUMAN	

	TF LBP-1b		TF LBP-1b	
	TFCP2	TFCP2		
	TRAP25		TRAP25	
p75 NTR-complex	p75 NTR	Cadherin EGF LAG seven-pass G-type receptor 2	Cadherin EGF LAG seven-pass G-type receptor 2	
		DKFZP586F1524 protein	DKFZP586F1524 protein	DKFZP586F1524 protein
		HYPOTHETICAL PROTEIN FLJ39249	HYPOTHETICAL PROTEIN FLJ39249	HYPOTHETICAL PROTEIN FLJ39249
		Nogo receptor	Nogo receptor	
		NRAGE/MAGED1	NRAGE/MAGED1	
		p75 NTR	p75 NTR	
		Rho-GDI	Rho-GDI	
		Thioredoxin domain-containing protein	Thioredoxin domain-containing protein	
		VAPA	VAPA	
Lamezin-complex	Lamezin	ASPH	ASPH	
		bzw1: basic leucine zipper and w2 domains 1	bzw1: basic leucine zipper and w2 domains zipper and w2	bzw1: basic leucine zipper and w2



			1	domains 1
	C7orf14		C7orf14	C7orf14
	CLNS1A		CLNS1A	
	CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)		CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)	
	CNTNAP1		CNTNAP1	
	COX5B		COX5B	
	COX6B		COX6B	
	COX6C		COX6C	
	CSG1cA-T		CSG1cA-T	CSG1cA-T
	DICER1		DICER1	
	dkfzp586c1924		dkfzp586c1924	dkfzp586c1924
	DREV1		DREV1	DREV1
	EC 6.3.2.19 (Fragment)		EC 6.3.2.19 (Fragment)	
	EIF2B2		EIF2B2	

	ensp000000258417		ensp000000258417	ensp000000258417
	EXTL2		EXTL2	EXTL2
	G2AN		G2AN	
	Galactosylgalactosylxylo sylprotein 3-beta- glucuronosyltransferase 3		Galactosylgalactosylxylo sylprotein 3-beta- glucuronosyltransferase e 3	
	HIV-1 Vpr-binding protein (Fragment)		HIV-1 Vpr-binding protein (Fragment)	HIV-1 Vpr-binding protein (Fragment)
	HPIP		HPIP	HPIP
	HSPC329 (Fragment)		HSPC329 (Fragment)	HSPC329 (Fragment)
	hyou1: hypoxia up- regulated 1		hyou1: hypoxia up- regulated 1	hyou1: hypoxia up- regulated 1
	Hypothetical protein FLJ34763		Hypothetical protein FLJ34763	Hypothetical protein FLJ34763
	Hypothetical protein KIAA0062 (Fragment)		Hypothetical protein KIAA0062 (Fragment)	Hypothetical protein KIAA0062 (Fragment)
	Hypothetical protein KIAA1500 (Fragment)		Hypothetical protein KIAA1500 (Fragment)	Hypothetical protein KIAA1500 (Fragment)

		HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT).		HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT).	HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT).
		HYPOTHETICAL PROTEIN.		HYPOTHETICAL PROTEIN.	HYPOTHETICAL PROTEIN.
		HYPOTHETICAL PROTEIN.		HYPOTHETICAL PROTEIN.	
		IGF2R		IGF2R	
		ITGAV		ITGAV	
		ITPR2		ITPR2	
		KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa		KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa	KIAA1250, homolog of rat kinase D- interacting substance of 220 kDa
		Lamezin/FKRP	Lamezin/FKRP		
		Laminin, gamma 1		Laminin, gamma 1	
		LPHH1		LPHH1	
		MAGEB4		MAGEB4	MAGEB4
		MGC5442		MGC5442	MGC5442
		Neural cell adhesion molecule L1		Neural cell adhesion molecule L1	

	Neurotrypsin		Neurotrypsin	
	Nuclear protein SDK3		Nuclear protein SDK3	
	PPIB		PPIB	
	Presenilin1	Presenilin1		
	PTDSS1		PTDSS1	
	Reelin		Reelin	
	SCG2		SCG2	
	SIMILAR TO HYPOTHETICAL PROTEIN SB153.		SIMILAR TO HYPOTHETICAL PROTEIN SB153.	SIMILAR TO HYPOTHETICAL PROTEIN SB153.
	Similar to RIKEN cDNA 1100001L14 gene (Fragment)	Similar to RIKEN cDNA 1100001L14 gene (Fragment)	Similar to RIKEN cDNA 1100001L14 gene (Fragment)	Similar to RIKEN cDNA 1100001L14 gene (Fragment)
	STRA6 isoform 1		STRA6 isoform 1	STRA6 isoform 1
	TLOC1		TLOC1	
	UGCGL2		UGCGL2	
	VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR		VESICULAR INTEGRAL- MEMBRANE PROTEIN VIP36 PRECURSOR	VESICULAR INTEGRAL- MEMBRANE PROTEIN VIP36 PRECURSOR

	Wolfraamin		Wolfraamin	Wolfraamin
APP-C59-complex	C59	C59		
	Copine III		Copine III	Copine III
	COPS3		COPS3	
	CPNE7		CPNE7	CPNE7
	CUL3		CUL3	
	Fe65	Fe65		
	Fe65L1	Fe65L1		
	GTF3C3		GTF3C3	
	NRD1		NRD1	
	S100 beta		S100 beta	
	TIP60	TIP60		
	USP11		USP11	
	X11beta	X11beta		
BRI/ITM2B-complex	APLP2		APLP2	
	APP		APP	
	CARBOXYPEPTIDASE D		CARBOXYPEPTIDAS E D	
	Contactin1		Contactin1	

		Delta-like homolog	Delta-like homolog	Delta-like homolog	Delta-like homolog
		DPP6 (DIPEPTIDYL AMINOPEPTIDASE- LIKE PROTEIN 6)	DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)	DPP6 (DIPEPTIDYL AMINOPEPTIDASE- LIKE PROTEIN 6)	DPP6 (DIPEPTIDYL AMINOPEPTIDASE- LIKE PROTEIN 6)
		Integral membrane protein 2B (ITM2B)	Integral membrane protein 2B (ITM2B)		
		ITM2C		ITM2C	

TABLE 2

## INDIVIDUAL PROTEINS OF THE COMPLEXES

Protein name	SEQ ID	IPI number	Molecular weight
APP	5	IPI00006608.1	86943
15 KDA SELENO- PROTEIN PRECURSOR.	127	IPI00030877.1	17743
27 KDA GOLGI SNARE PROTEIN.	133	IPI00023135.1	24775
ACE	1	IPI00025852.1	149715
ADAMTS1	75	IPI00005908.1	105384
ADAMTS19	76	IPI00152639.1	134062
ADAMTS7	77	IPI00007692.1	109695
ALPHA-CENTRACTIN.	31	IPI00029468.1	42614
ALPHA-SOLUBLE NSF ATTACHMENT PROTEIN.	134	IPI00009253.1	33247
AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING FAMILY B MEMBER 1.	135	IPI00010843.1	77244
AOP2	178	IPI00024912.1	24904
APG-1	2	IPI00032918.1	94505
APLP1	3	IPI00020012.2	72176
APLP1	42	IPI00020012.1	72176
APLP2	4	IPI00031030.1	86956
APOD	117	IPI00006662.1	21276

ApoE receptor 2	6	IP100005774.1	105716
APP	5	IP100006608.1	86943
APP-C99	128	CZB00000004.1	11277.92
Archvillin	7	IP100170232.1	243162
ASPH	194	IP100029224.1	85498
BACE1	129	IP100011518.1	55764
BACE2	175	IP100001954.1	56180
BCL2/ADENOVIRUS E1B 19KD-INTERACTING PROTEIN 1, ISOFORM BNIP1.	136	IP100014022.1	26217
BET1	137	IP100025163.1	13289
bzw1: basic leucine zipper and w2 domains 1	236	IP100005681.1	48043
C59	239	CZB000000003.1	6834.89
C7orf14	195	IP100022495.1	228049
Cadherin EGF LAG seven-pass G-type receptor 2	157	IP100015346.1	317453
CALD1	118	IP100011878.1	64256
CALPAIN SMALL SUBUNIT.	138	IP100025084.1	28316
CALR	119	IP100020599.1	48142
Calsynenin 1	158	IP100007257.1	109793
CARBOXYPEPTIDASE D	246	IP100027078.2	152915
CASPASE-14 PRECURSOR.	32	IP100013885.1	27680
CD11a/CD18 INTEGRIN, BETA-2	120	IP100007039.1	84791
CDC42BPB	43	IP100005689.2	199210



CENTROMERE/KINETOCHORE PROTEIN ZW10 HOMOLOG.				
CGI-13	139	IP100011631.1	88829	
CHRNA5	156	IP100008847.1	52917	
CLNS1A	78	IP100105403.1	53311	
CLU: clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)	196	IP100004795.1	26215	
	197	IP100219642.1	55192	
CNTNAP1	198	IP100219249.1	164756	
Contactin1	12	IP100029751.1	113320	
COP9	44	IP100009480.1	23226	
COP9 COMPLEX SUBUNIT 4.	45	IP100163757.1	46378	
COP9 complex subunit 7a	46	IP100033154.1	30277	
Copine III	241	IP100024403.1	60131	
COPS3	47	IP100025721.1	47873	
COPS5	48	IP100009958.3	37452	
COPS6: COP9 subunit 6 (MOV34 homolog, 34 kD)	49	IP100163230.1	33576	
COPS7B	50	IP100009301.1	29622	
COX5B	199	IP100021785.2	13696	
COX6B	200	IP100216085.1	10192	
COX6C	201	IP100015972.1	8781	
CPNE7	240	IP100002657.1	70294	

CRK	8	IP100004838.1	33872
CRKL	9	IP100004839.1	33777
CRTAP	79	IP100007384.1	46562
CSG1cA-T	86	IP100018606.1	87640
CSNK1D	10	IP100011102.1	47330
CSNK1E	11	IP100027729.1	47315
CU70_HUMAN	80	IP100027898.3	25456
CUL3	51	IP100014312.1	88930
DAB1	13	IP100026889.2	59979
DAB2IP	14	IP100045600.1	117651
DCTN1	33	IP100011446.1	127404
DEC1	81	IP100003482.1	36068
Delta-6 fatty acid desaturase	159	IP100003544.1	52259
Delta-like homolog	160	IP100009191.1	41143
DICER1	202	IP100012680.1	217628
dkfzp586c1924	237	IP100031064.1	21527
DKFZP586F1524 protein	95	IP100165506.1	42031
DLG1	67	IP100002554.1	103221
DNAJB1	15	IP100015947.1	38044
DNAJC3	82	IP100006713.1	57580
DPP6 (DIPEPTIDYL AMINOPEPTIDASE-LIKE PROTEIN 6)	247	IP100000823.1	97588

DREV1		203	IP100100239.1	36536
Dynactin 3, isoform 2		34	IP100013654.1	19469
DYNACTIN COMPLEX 50 KDA SUBUNIT.		140	IP100013802.1	44231
EC 6.3.2.19 (Fragment)		204	IP100028307.1	143477
EIF2B2		205	IP100028083.1	38990
ELAVL1		105	IP100019360.2	36092
ensp00000258417		238	IP100216484.1	75579
Epim		106	IP100031034.1	33312
ERP70		83	IP100009904.1	72932
EXTL2		206	IP100002732.1	37466
Fe65		135	IP100010843.1	77244
Fe65L1		242	IP100023841.1	81080
Fe65L2		53	IP100032785.1	52638
FIGF		107	IP100004653.1	40444
Filamin, gamma		108	IP100165017.1	291151
FLJ10474		176	IP100163721.1	199210
fij11198, member of the abc transporter family		183	IP100019973.2	79745
FLJ12599		52	IP100182757.1	102917
FLJ14787		177	IP100102685.1	35274
FLJ30668		161	IP100043733.1	33338
FLJ39249		162	IP100167501.1	27459
G2AN		207	IP100011454.1	109438

Galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 3			
GBTS1	208	IP100014931.1	37062
GOLGA3	84	IP100002919.2	22329
GP25L2 PROTEIN.	109	IP100158673.1	170268
GPR49	141	IP100030888.1	25122
GPS1	54	IP100021131.1	99998
GRCB	55	IP100156282.1	56481
GTF3C3	85	IP100003407.1	62265
HARP11, UNCHARACTERIZED HYPOTHALAMUS PROTEIN.	243	IP100015806.1	101272
HIV-1 Vpr-binding protein (Fragment)	35	IP100016170.2	47060
HPIP	209	IP100155567.1	169450
HSPC009.	210	IP100100773.1	80643
HSPC329 (Fragment)	142	IP100022277.1	11731
Hunc18a	211	IP100000205.1	18247
hyou1: hypoxia up-regulated 1	110	IP100046057.1	68736
HYPOTH 61.5 KDA PROTEIN (FRAGMENT).	103	IP100000877.1	111335
HYPOTH 78.2 KDA PROTEIN (FRAGMENT).	143	IP100107712.1	61548
HYPOTHETICAL PROTEIN (FRAGMENT).	144	IP100141564.1	78194
hypothetical protein BC013764	68	IP100166518.1	112183
hypothetical protein FLJ11151	116	IP100060715.1	35701
HYPOTHETICAL PROTEIN FLJ12599.	30	IP100019937.1	35622
	52	IP100182757.1	102917

Hypothetical protein FLJ31432	16	IP100102281.1	36961
Hypothetical protein FLJ34763	215	IP100168126.1	50520
HYPOTHETICAL PROTEIN FLJ35393.	69	IP100167994.1	21530
HYPOTHETICAL PROTEIN FLJ39249	162	IP100167501.1	27459
Hypothetical protein KIAA0062 (Fragment)	216	IP100014236.1	58417
Hypothetical protein KIAA1402 (Fragment)	86	IP100018606.1	87640
Hypothetical protein KIAA1500 (Fragment)	217	IP100151706.2	126320
HYPOTHETICAL PROTEIN KIAA1524 (FRAGMENT).	214	IP100001627.1	99841
HYPOTHETICAL PROTEIN.	212	IP100028427.1	44941
HYPOTHETICAL PROTEIN.	213	IP100015506.1	15066
IGF2R	218	IP100007226.1	274309
Integral membrane protein 2B (ITM2B)	249	IP100031821.1	30338
Integral membrane transporter protein	173	IP100020093.1	31735
ISL1	17	IP100025071.1	39036
ISLET-BRAIN 2.	36	IP100009277.1	84711
ITCH	163	IP100061780.1	102803
ITGA1	18	IP100008244.1	127838
ITGAV	219	IP100027505.1	116052
ITGB1	19	IP100009465.1	88465
ITM2C	248	IP100185968.1	33329
ITPR2	220	IP100031545.1	308078

JIP-1		37	IP100023133.1	77524
JNK		38	IP100129682.1	44229
KIAA1102 (Fragment)		70	IP100160387.1	121739
KIAA1102 PROTEIN (FRAGMENT).		56	IP100167860.1	123943
KIAA1250, homolog of rat kinase D-interacting substance of 220 kDa		164	IP100033429.1	197211
KIAA1949 (FRAGMENT)		71	IP100152853.1	73064
Kif5c		41	IP100028561.1	109495
kinectin 1 (kinesin receptor)		174	IP100032968.1	156093
KINESIN HC		39	IP100012837.1	109685
KINESIN LC1.		40	IP100020096.1	64786
LAMB1		87	IP100013976.1	198066
Lamezin/FKRP		222	IP100013281.1	54568
Laminin, gamma 1		88	IP100003398.1	177607
LBP-9		184	IP100005099.1	54627
LDLR		20	IP100000070.1	95376
LPHH1		221	IP100017562.1	157178
MAGEB4		223	IP100006737.1	38923
MAPK8IP3/JIP3		21	IP100045524.1	147789
MDS032, UNCHARACTERIZED HEMATOPOIETIC STEM/PROGENITOR CELLS PROTEIN.		145	IP100020515.1	29345
MGC5442		224	IP100027773.1	26261

MT-ACT48		89	IP100032410.1	46355
NEDD5		22	IP100014177.1	41487
NEDD8		57	IP100020008.1	9072
Neural cell adhesion molecule L1		225	IP100027087.1	140003
NEUROBLASTOMA-AMPLIFIED PROTEIN.		146	IP100026324.1	152546
Neurotrypsin		91	IP100011063.1	97012
Nicastrin		165	IP100021983.1	78411
Nogo receptor		190	IP100220122.1	54053
Nogo-A		166	IP100021766.3	129931
NOTCH4-like protein (Hypothetical protein)		90	IP100007830.1	29618
NRAGE/MAGED1		189	IP100001829.2	86151
NRD1		244	IP100014521.1	130945
Nuclear protein SDK3		226	IP100099225.1	81584
OPA1		121	IP100107749.1	111822
p75 NTR		193	IP100027436.1	45183
Paladin		179	IP100161782.1	96754
PAWR		111	IP100001871.1	36766
PC7		130	IP100002882.1	86247
PCDH16		92	IP100064262.1	346181
PDGFRB		167	IP100015902.1	123968
Phosphatidylserine receptor		147	IP100027294.1	47939
Pilt		72	IP100010544.2	60705

PLK		23	IP100021248.1	68255
PLOD		93	IP100027192.1	83580
PLOD3		94	IP100030255.1	84785
PPIB		227	IP100107117.1	23743
Presenilin1		123	IP100026333.1	52163
Protocadherin beta 7		132	IP100001425.1	86707
Protocadherin gamma C3		58	IP100001872.3	101077
Proto-oncogene tyrosine kinase FYN (P59-FYN, SYN, SLK) isoform 1		24	IP100031350.1	63754
PTDSS1		228	IP100010746.1	55528
PTK7		168	IP100012719.1	118260
PTPN1		131	IP100216465.1	54452
PUTATIVE DNA POLYMERASE DELTA P38 SUBUNIT.		95	IP100165506.1	42031
PYCS		122	IP100008982.1	87302
q8wvi0		104	IP100103133.1	13878
QPRT		25	IP100015791.2	30816
RAB39, MEMBER RAS ONCOGENE FAMILY.		96	IP100167108.1	25007
RAB6A		124	IP100023526.1	23593
RAD50-INTERACTING PROTEIN 1.		148	IP100072224.1	93442
RAP1, GTP-GDP dissociation stimulator 1		125	IP100107875.1	66331
RBX1		59	IP100003386.1	12274
Reelin		97	IP100021018.1	388402



RHOBTB1	60	IP100001317.1	79417
RHOBTB2	61	IP100008545.2	85137
Rho-GDI	191	IP100003815.1	23207
RR42_HUMAN	185	IP100014198.2	31835
S-100 beta	26	IP100220413.1	10713
SC65	98	IP100023337.1	50381
SCG2	229	IP100009362.1	70869
SEC22B VESICLE TRAFFICKING PROTEIN	149	IP100006865.1	24741
SERPINA1	169	IP100032180.1	46737
SIM TO CGI-20	62	IP100144290.1	36504
SIM TO PLEXIN 1 - MOUSE.	27	IP100164586.1	208223
SIM TO Y71H10A. 2.P.	170	IP100170775.1	68184
Similar to BCL2-associated athanogene 2 (Hypothetical protein)	180	IP100130304.1	23474
Similar to golgi SNAP receptor complex member 1	153	IP100044920.1	20068
Similar to hydroxysteroid 17-beta dehydrogenase 11	100	IP100122464.1	33518
Similar to hypothetical protein FLJ22329	101	IP100002905.1	28319
SIMILAR TO HYPOTHETICAL PROTEIN SB153.	230	IP100084084.3	86438
SIMILAR TO POL POLYPROTEIN.	63	IP100093098.2	155047
Similar to RIKEN cDNA 1100001L14 gene (Fragment)	232	IP100062859.1	40583

Similar to RIKEN cDNA 1300010F03 gene			
Sortilin-related receptor	99	IP100122560.1	116226
STMN3	171	IP100022608.1	248441
STRA6 isoform 1	73	IP100021199.2	21017
STX10	231	IP100154566.1	73533
STX1A	150	IP100012264.2	28114
STX1B2	112	IP100003370.1	33023
STX3A	113	IP100065786.1	33245
SYNTAXIN 10.	114	IP100012421.1	33141
SYNTAXIN 18.	150	IP100012264.2	28114
SYNTAXIN 5.	151	IP100027194.1	38674
Telencephalin	152	IP100012005.1	34086
TF LBP-1b	126	IP100019003.2	97331
TFCP2	186	IP100005018.1	60491
TGM5	187	IP100029650.1	57313
Thioredoxin domain-containing protein	28	IP100003518.1	71919
TIP60	172	IP100001028.1	32535
TLOC1	245	IP100024400.1	58681
TNRC6	233	IP100019004.1	45862
TRAP25	181	IP100158479.1	210272
TRIP15	188	IP100063213.1	20277
TUBGCP3	64	IP100018813.1	51597
	65	IP100033516.1	103571

UGCGL2		102	IP100024467.1	174761
USP11		66	IP100184533.1	109817
USP7		182	IP100003965.1	128272
VAPA		192	IP100170692.1	27318
VESICULAR INTEGRAL-MEMBRANE PROTEIN VIP36 PRECURSOR		234	IP100009950.1	40229
VESICULAR-FUSION PROTEIN NSF.		154	IP100006451.1	82654
VLDL receptor		29	IP100024273.1	96098
VTRP		155	IP100001643.1	72480
Wolframin		235	IP100008711.1	100306
X11alpha		115	IP100025752.1	92924
X11beta		74	IP100017817.1	82512

TABLE 3

## BIOCHEMICAL ACTIVITIES OF THE COMPLEXES

Name of Complex	Biochemical activity
APP-C59-complex	APP signaling activity (regulator of transcription)
Bace1-complex	APP processing beta-secretase
Bace2-complex	APP processing beta- and alpha-secretase
BRI-complex	Regulator of BRI and/or APP processing and/or signaling
Dab1-complex	Regulator of APP processing and/or signaling; Upstream activator of tau phosphorylation
Fe65L2-complex	Regulator of APP turnover, processing and signaling
Pit1-complex	Regulator of X11beta function and of APP processing and/or signaling
Paladin-complex	Regulator of X11beta function and of APP processing and/or signaling
Neurotrypsin-complex	Regulator of APP processing secretases
Hunc18a-complex	Regulator of secretory vesicular transport
Telencephalin-complex	Gamma-secretase activity and assembly (trafficking)
PC7-complex	Regulator of alpha- and beta-secretase activity
TFCP2-complex	Regulator of APP signaling activity (regulator of transcription)
Jip1-complex	Regulator of APP trafficking and signaling
Lamezin-complex	Regulator of protein glycosylation and phospholipid metabolism
VTRP-complex	Regulator of vesicular transport between endoplasmic reticulum and Golgi

P75 NTR

Apoptosis related signalling

TABLE 4

## MEDICAL APPLICATIONS OF THE COMPLEXES

Complex	Medical application
mDAB1	neurodegenerative disease such as Alzheimer's disease;
JIP1	neurodegenerative disease such as Alzheimer's disease and related disorders;
Fe65L2	neurodegenerative disease such as Alzheimer's disease; cancer such as prostate cancer and breast cancer and skin cancer
Pilr/TJP4	neurodegenerative disease such as Alzheimer's disease; inflammatory conditions such as ulcerative colitis, Crohn's disease and arteriosclerosis
Neurotrypsin	neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders
Hunc18a	neurodegenerative disease such as Alzheimer's disease and related disorders;
Telencephalin	neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders
PC7	neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders;
VTRP	neurodegenerative disease such as Alzheimer's disease;
BACE1 (new)	neurodegenerative diseases such as Alzheimer's disease and related neurodegenerative disorders
BACE2	neurodegenerative disease such as Alzheimer's disease;
PALADIN	neurodegenerative disease such as Alzheimer's disease;

TFCP2	neurodegenerative disease such as Alzheimer's disease;
p75 NTR	neurodegenerative disease such as Alzheimer's disease;
Lamezin	neurodegenerative disease such as Alzheimer's disease, congenital muscular dystrophy 1C and limb-girdle muscular dystrophy 2;
APP-C59	neurodegenerative disease such as Alzheimer's disease;
BRI/ITM2B	neurodegenerative disease such as Alzheimer's disease and familial British dementia;

**SEQUENCES**

SEQ ID No:1

MGAASGRRGPGLLLPLLLLLPPQPALALDPGLQPGNFSADEAGAQLFAQSYNSSAE  
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 GEMEVD

SEQ ID No:3

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MQI

SEQ ID No:5

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SEQ ID No:9

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HR

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RNPEDVDRERREHEREERMGQLRGSATRALPPGPPTGATANRLRSAAPVASTPASRI  
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GK

SEQ ID No:12

MKMWLLVSHLVIISITTCLAEFTWYRRYGHGVSEEDKGFGPIFEEQPINTIYPEESLEGKV  
SLNCRARASFPFVYKWRMNNGDVDLTSDRYSMVGGNLVINNPDKQKDAGIYYCLASN  
NYGMVRSTEATLSFGYLDPPPEERPEVRVKEGKGMVLLCDPPYHFPDDL SYRWLLNE  
FPVFITMDKRRFVSQTNGNLYIANVEASDKGNYSFCVSSPSITKSVFSKFIPLIPERTTK  
PYPADIVVQFKDVYALMGQNVTLCEFALGNPVPDIRWRKVLEPMPSTAEISTSGAVLKIF  
NIQLEDEGIYECEAENIRGKDKHQARIYVQAFPEWVEHINDTEVDIGSDLYWPCVATGKP  
IPTIRWLKNGYAYHKGELRLYDVT FENAGMYQCIAENTYGAIYANAELKILALAPTFEMN  
PMKKKILAAKGGRVIIIECKPKAAPKPKFSWSKGT EWL VNSSRILIWEDGSLEINNITRND  
GGIYTCFAENNRGKANSTGTLVITDPTRIILAPINADITVGENATMQCAASFDPALDLTFV  
WSFNGYVIDFNKENIHYQRNFMLDSNGELLIRNAQLKHAGRYTCTAQTIVDNSSASADL  
VVRGPPGPPGGLRIEDIRATSVALTWSRGS DNHSPISKYTIQTKTILSDDWKDAKTDPPII  
EGNMEAAARAVDLIPWMEYEF RVVATNTLGRGEP SIPS NRIKTDGAAPNVAPSDVGGGG  
GRNRELTITWAPLSREYHYGNNFGYIVAFK PFDGEEWKKVTVTNPD TGRYVHKDETMS  
PSTAFQVKVKAFNNKGDGPYSLVAVINSAQDAPSEAPTEVGKVLSSSEISVHWEHVLE  
KIVESYQIRYWAAHDKEEAANRVQVTSQEYSARLENLLPDTQYFIEVGACNSAGCGPPS  
DMIEAFTKKAPPSQPPRISSVRSGSRYIITWDHVVALSNESTVTGYKVLYRPDGGQHDGK  
LYSTHKHSIEVPIPRDGEYVVEVRAHSDGGDGVVSQVKISGAPTLSPSLLGLLLPAFGILV  
YLEF

SEQ ID No:13

MSTETELQVAVKTSAKKDSRKKGQDRSEATLIKRFKGEGVRYKAKLIGIDEVSAARGDK  
LCQDSMMKLKGVVAGARSKGEHKQKIFLTISFGGIKIFDEKTGALQHHHAVHEISYIAKDI  
TDHRAFGYVCGKEGNHRFVAIKTAQAAEPVILDLRDLFQLIYELKQREELEKKAQKDKQ  
CEQAVYQTILEEDVEDPVYQYIVFEAGHEPIRDPETEENIYQVPTSQKKEGVYDVPKSQL  
PVSAVTQLELFGDMSTPPDITSPPTPATPGDAFIPSSSQTLPASADVFSVPLGTAAVPP  
GYVAMGAVLPSFWGQQPLVQQQMVMGAHPPVAQVMPGAQPIAWGQPGLFPATQQP  
WPTVAGQFPPAAFMPTQTVMPL  
PAAMFQGGLTPLATVPGTSDSTRSSPQTDKPRQKMGKETFKDFQMAQPPPVPSPKPD  
QPSLTCTSEAFSSYFNKVGVAQDTHDCDDFDISQLNLTPVTSTTPSTNSPPTPAPRQSS  
PSKSSASHASDPTTDDIFEFGFESPSKSEEQEAPDGSQASSNSDPFGEPSPGEPDNI  
SPQDGS

SEQ ID No:14

MPRLKESRSHESELLSPSSAVEALDLSMEEVVIKPVHSSILGQDYCFEVTTS SSGSKCFS  
CRSAAERDKWMENLRRVHPNKNDSRRVEHILKLWVIEAKDLPAKKKYLCELCLDDVL  
YARTTGKLKTDNVFWGEHFEFHNLPPLRTVTVHLYRETDK KKKKERN SYLGLVSLPAAS  
VAGRQFVEKWYPVVTNPNKGGKGP GPMIRIKARYQTITILPMEYKEFAEHITNHYLGL  
CAALEPILSAKTKEEMASALVHILQSTGKVKDFLTDLMMSEVDRCGDNEHLIFRENTLAT  
KAIEEYLKLVGQKYLQDALGEFIKALYESDENCEVDPSKCSAADLPEHQGNLKMCCELA  
FCKIINSYCVFPRELKEVFASWRQECSSRGRPDISERLISASLFLRFLCPAIMSPSLFNLL  
QEYPDDRTARTLTIAKVTQNLANFAKFGSKEEYMSFMNQFLEHEWTNMQRFLLEISNP  
ETLSNTAGFEGYIDLGRELSSLHSLLWEAVSQLEQSIVSKLGPLPRILRDVHTALSTPGS  
GQLPGTNDLASTPGSGSSSISAGLQKMVIENDLSGLIDFTRLPSPTPENKDLFFVTRSSG  
VQPSPARSSSYSEANEPDLQMANGGKSLSMVDLQDARTLDGEAGSPAGPDVLPDGGQ  
AAAAQLVAGWPARATPVNLAGLATVRRAGQTPPTPGTSEGAPGRPQLLAPLSFQNPVY  
QMAAGLPLSPRGLGDSGSEGHSSLSHSNSEELAAAALGSGFSTAAEELARRPGELAR  
RQMSLTEKGGQPTVPRQNSAGPQRRIDQPPPPPPPPPPAPRGRTPPNLLSTLQYPRP  
SSGTLASASPDWVGPPSTRLRQQSSSSSKGDSPELKPRAVHKQGPSPVSPNALDRTAAW  
LLTMNAQLLEDEGLGPDPPHRDRLRSKDELSQAEKDLAVLQDKLRISTKKLEEYETLFK  
CQEETTQKLVLEYQARLEEGERLRRQQEDKDIQMKGIISRLMSVEEELKKDHAEMQA  
AVDSKQKIIDAQEKRIASLDAANARLMSALTQLKERYSMQARNGISPTNPTKLQITENGE  
FRNSSNC

SEQ ID No:15

MGKDYYQTLGLARGASDEEIKRAYRRQALRYHPDKNKEPGAEEKFKEIAEAYDVLSDP  
RKREIFDRYGE EGLKGSGPSGGSGGGANGTSFSYTFHGD PHAMFAEFFGGRNPFDTF  
FGQRNGEEGMDIDDPFSGFPMGMGGFTNVNFGRSRSAQEPARKKQDPPVTHDLRVS  
LEEIYSGCTKKMKISHKRLNPDGKSIRNEDKILTIEVKKGWKEGTKITFPKEGDQTSNNIP  
ADIVFVLKDKPHNIFKRDGSDVIYPARISLREALCGCTVNVPTLDGRTIPVVKDVIRPGM  
RRKVPGEGLPLPKTPEKRGDLIEFEVIFPERIPQTSRTVLEQVLPI

SEQ ID No:16

MGSPGASLGIIKKALQSEQATALPASAPAVSQPTAPAPSCLPKAGQVIPALLREAPFSSVI  
APTLGCGFLFLAWVAAEVPEESSRMAGSGARSEEGRRQHAFVPEPFDGANVVPNLWL  
HSFEVINDLNHWHDHITKLRLKESLRGEALGVYNRLSPQDQGDYGTVKEALLKAFGVPG  
AAPSHLPKEIVFANS MGKGYLKGKIGKVPVRFLVD SGAQVSVVHPNLWEEVTDGDLD  
TLQPFENVVKVANGAEMKILGVWDTAVSLGKLKKAQFLVANASAEAAIGTDVLQDHN  
AILDFEHRTCTLKGKKFRLLPVGGSLEDEFDLELIEEDPSSEEGRQELSH

SEQ ID No:17

MGDMGDPPKKKRLISLCVGCNQHIDQYILRVSPDLEWHAACLKCAECNQYLDESCTC  
FVRDGKTYCKRDYIRLYGIKCAKCSIGFSKNDFVMRARSKVYHIECFRCVACSRQLIPGD  
EFALREDGLFCRADHDVVERASLGAGDPLSPLHPARPLQMAAEPISARQPALRPHVHK  
QPEKTTRVRTVLNEKQLHTLRTCYAANPRPDALMKEQLVEMTGLSPRVIRVWFQNKRC  
KDKKRSIMMKQLQQQQPNDKTNIQGMTGTPMVAASPERHDGGLQANPVEVQSYQPP  
WKVLSDFALQSDIDQPAFQQLVNFSEGGPGSNSTGSEVASMSSQLPDTPNMVASPIE  
A

SEQ ID No:18

FNVDVKNSMTFSGPVEDMFGYTVQQYENEEGKWVLIGSPLVGQPKNRTGDVYKCPVG  
RGESLPCVKLDLPVNTSIPNVTEVKENMTFGSTLVNPNNGGFLACGPLYAYRCGHLHYT  
TGICSDVSPTFQVVNSIAPVQECSTQLDIVIVLDGSNSIYPWDSVTAFLNDLLKRMDIGPK  
QTQVGIVQYGENVTHEFNLNKYSSTEEVLVAAKKIVQRGGRQTM TALGTD TARKEAFTE  
ARGARRGVKKVMVIVTDGESHDNHRLKKVIQDCEDENIQRFSIAILGSYNRGNLSTEK FV  
EEIKSIASEPTEKHFFNVSD ELALVTIVKTLGERIFALEATADQSAASFEMEMSQTGFSAH  
YSQDWVMLGAVGAYDWNGTVVMQKASQIIIPRNTTFNVESTKKNEPLASYLGYTVNSA

TASSGDVLYIAGQPRYNHTGQVIIYRMEDGNIKILQTLSGEQIGSYFGSILTTTDDIDKDSNT  
 DILLVGAPMYMGTEKEEQGKVYVYALNQTRFEYQMSLEPIKQTCCSSRQHNSCTTENK  
 NEPCGARFGTAIAAVKDLNLDGFNDIVIGAPLEDDHGGAVYIYHGSGKTIRKEYAQRIPS  
 GGDGKTLKFFGQSIHGEMDLNGDGLTDVTIGGLGGAALFWSRDVAVVKVTMNFEPNKV  
 NIQKKNCHMEGKETVCINATVCFEVKLKSKEDTIYEADLQYRVTLDSLRLQISRSFFSGTQ  
 ERKVQRNITVRKSECTKHSFYMLDKHDFQDSVRITLDFNLDPENGPVLDDSLPNSVHE  
 YIPFAKDCGNKEKCISDLSLHVATTEKDLLIVRSQNDKFNVS�TVKNTKDSAYNTRTIVHY  
 SPNLVFSGIEAIQKDSCESNHNITCKVGYPFLRRGEMVTFKILFQFNTSYLMENVTIYLSA  
 TSDSEEPPELSDNVVNISIPVKYEVGLQFYSSASEYHISIAANETVPEVINSTEDIGNEINI  
 FYLIRKSGSFPMPELKLSSISFPNMTSNGYPVLYPTGLSSSENANCRPHIFEDPFSINSKG  
 KMTTSTDHLKRGITLDCNTCKFATITCNLTSSDISQVNVSLILWKPTFIKSYFSSLNLTIRG  
 ELRSENASLVLSASNQKRELAIQISKDGLPGRVPLWVILLSAFAGLLLLMLLILALWKIGFF  
 KRPLKKKMEK

SEQ ID No:19

MNLQPIFWIGLISSVCCVFAQTDENRCLKANAKSCGECIQAGPNCGWCTNSTFLQEGM  
 PTSARCDLEALKKKKGCPPDDIENPRGSKDIKKNKNVTNRSGKTAELKPKEDIHQIQPQ  
 QLVLRRLRSGEPQTFTLKFKRAEDYPIDLYYLMDSLYSMKDDLENVKSLGTDLMNEMRRI  
 TSDFRIGFGSFVEKTVMPYISTTPAKLRNPCTSEQNCTTPFSYKNVLSLTNKGEVFNELV  
 GKQRISGNLDSPEGGFDAQVAVCGSLIGWRNVTRLLVFSTDAGFHFAGDGKLGIVL  
 PNDGQCHLENMYTMSHYDYPSIAHLVQKLSENNIQTIFAVTEEFQPVYKELKNLIPKS  
 AVGTLSANSSNVIQLIIDAYNSLSSEVILENGKLSEGVITISYKSYCKNGVNGTGENGRC  
 SNISIGDEVQFEISITSNKCCKDSDFSIRPLGFTEEEVILQYICECECQSEGIPEPKC  
 HEGNGTFECGACRCNEGRVGRHCECSTDEVNSEDMDAYCRKENSSEICSNNGECVC  
 GQCVCRKRDNTNEIYSGKFCECDNFNCDRSNGLICGGNGVCKCRVCECNPNYTGSAC  
 DCSLDTSTCEASNGQICNGRGICECGVCKCTDPKFQGGQTCEMCQTCLGVCAEHKECV  
 QCRAFNGKEKDTCTQECSYFNITKVESRDKLPQPVQPDVSHCKEKDVDDCWFYFT  
 YSVNGNNEVMVHVVENPECPTGPDIIPIVAGVVAGIVLIGLALLLIWKLLMIHDRREFAKF  
 EKEKMNAKWDTGENPIYKSAVTTVVNPKYEGK

SEQ ID No:20

MGPWGWKLRTVALLLAAAGTAVGDRCERNEFQCQDGKCSYKWVCDGSAECQDG  
 SDESQETCLSVTCKSGDFSCGGRVNRCPQFWRCQDQVDCDNGSDEQGCPPKTCNQ  
 DEFRCHDGKCSIRQFVCDSDRDCLDGSDEASCPVLTCGPASFQCNSSSTCIPQLWACD



NDPDCEDGSDEWPQRCRGLYVFQGDSSPCSAFEFHCLSGECIHSSWRCDGGPDCKD  
KSDEENCAVATCRPDEFQCSDGNCIHGSRQCDREYDCKDMSDEVGCVNVTLCCEGPN  
KFKCHSGECITLDKVCNMARDCRDWSDEPIKECGTNECLDNNGGCSHVCNDLKIGYEC  
LCPDGFQLVAQRRCEDIDECQDPDTCSQLCVNLEGGYKCQCEEGFQLDPHTKACKAV  
GSIAYLFFTNRHEVRKMTLDRSEYTSILIPNLRNVVALDTEVASNRIYWSDLQRMICSTQ  
LDRAHGVSSYDTVISRDIQAPDGLAVDWIHSNIYWTDSVLGTVSVADTKGVKRKTLFRE  
NGSKPRAIVVDPVHGFMYWTDWGTPAKIKKGGLNGVDIYSLVTENIQWPNGITLDLLSG  
RLYWVDSKLHSSIDVNGGNRKTILEDKRLAHPFSLAVFEDKVFWDIINEAIFSANRL  
TGSDVNLLAENLLSPEDMVLFHNLTPRGVNW CERTTSLNNGGCQYLCLPAPQINPHSP  
KFTCACPDGMILLARDMRSCLTEAAAVATQETSTVRLKVSSTAVRTQHTTTTRPVPDTS  
RLPGATPGLTTVEIVTMSHQALGDVAGRGNEKKPSSVRALSIVLPVLLVFLCLGVFLLW  
KNWRLKNINSINFDPVYQKTTEDEVHICHNQDGYSYPSRQMVSLLEDDVA

SEQ ID No:21

MMEIQMDEGGGVVVYQDDYCSGSVMSEVSGLAGSIYREFERLIHCYDEEVVKELMPL  
VVNVLENLDSVLSENQEHEVELELLREDNEQLLTQYEREKALRRQAEEKFIEFEDALEQ  
EKKELQIQVEHYEFQTRQLELKAKNYADQISRLEERESEMKKEYNALHQRHTEMIQTYV  
EHIERSKMQQVGGNSQTESSLPGRSRKERPTSLNVFPLADGTVRAQIGGKLVPAGDH  
WHLSDLGQLQSSSSYQCPQDEMSESGQSSAAATPSTTGTKSNTPTSSVPSAAVTPLN  
ESLQPLGDYGVGSKNSKRAREKRDSRNMEVQVTQEMRNVSIGMGSSDEWSDVQDIID  
STPELDMCPETRLDRTGSSPTQGIVNKAFGINTDSLYHELSTAGSEVIGDVDEGADLLG  
ETSAPSVSGMGKEVGNLLLENSQLLETKNALNVVKNDLIAKVDQLSGEQEVL RGELEAA  
KQAKVKLENRIKELEEELKRVKSEAIARREPKEEAEDVSSYLCTESDKIPMAQRRRFRTR  
VEMARVLMERNQYKERLMELQEAVRWTE MIRASREHPSVQEKKKSTIWQFFSRLFSSS  
SSPPPAKRPYPVSVNIHYKSPTTAGFSQRRNHAMCPI SAGSRPLEFFPDDCTSSARRE  
QKREQYRQVREHVRNDDGRLQACGWSLPAKYKQLSPNGGQEDTRMKNVPVPVYCRP  
LVEKDPTMKLWCAAGVNL SGWRPNEDDAGNGVKPAPGRDPLTCDREGDGEPKSAHT  
SPEKKKAKELPEMDATSSRVWILTSTLTTSKVVIIDANQPGTVVDQFTVCNAHVLCISSIP  
AASDSYPPGEMFLDSDVNPEDPGADGVLAGITLVGCATRCNVPRSNCSRGDTPVLD  
KGQGEVATIANGKVNPSQSTEEATEATEVPDPGPSEPETATLRPGPLTEHVFTDPAPTP  
SSGPQPGSENGPEPDSSSTRPEPEPSGDPTGAGSSAAPT MWLGAQNGWLYVHSAVA  
NWKKCLHSIKLKDSVLSLVHVKG RVLVALADGT LAIFHRGEDGQWDLSNYHLM DLGHP  
HHSIRCM AVVYDRVWCGYKNKVHV IQPKTMQIEATMTPQKSFDAHPRRESQVRQLAWI  
GDGVVWSIRLDSTLRLYHAHTHQHLQDV DIEPYVSKMLGTGKLGFSFVRITALLVAGSR

LWVGTGNGVVISIPLTETVVLHRGQLLGLRANKTSPTS GEGARPGGIIHVYGDDSSDRA  
ASSFIPYCSMAQAQLCFHGHHRDAVKFFVSVPGNVLATLNGSVLDSPAEGPGPAAPASE  
VEGQKLRLNVLVLSGGEGYIDFRIGDGEDDETEEGAGDMSQVKPVL SKAERSHIIVWQV  
SYTPE

SEQ ID No:22

MSKQQPTQFINPETPGYVGFANLPNQVHRKSVKKGFEFTLMVVGESGLGKSTLINSFL  
TDLYPERVIPGAAEKIERTVQIEASTVEIEERGVLRLTVVDTPGYGDAINCRDCFKTIISYI  
DEQFERYLHDESGLNRRHIIDNRVHCCFYFISPFHGHLKPLDVAFMKAIHNKVNIVPVIK  
ADTLTLKERERLKKRILDEIEEHNIKIYHLPDAESDEDEDFKEQTRLLKASIPFSVVGSNQL  
IEAKGKKVRGRLYPWGVVEVENPEHNDFLKLRTMLITHMQDLQEVTQDLHYENFRSER  
LKRGGRKVENEDMNKDQILLEKEAELRRMQEMIARMQAQMOMQMGGDGDGGALG  
HHV

SEQ ID No:23

MSAAVTAGKLARAPADPGKAGVPGVAAPGAPAAAPPAKEIPEVLVDPRSRRRRYVRGRF  
LGKGGFAKCFEISDADTKEVFAGKIVPKSLLLKPHQREKMSMEISIHRS LAHQHVVG FHG  
FFEDNDFV FVVLELCRRRS LLELHKRRKALTEPEARYYLRQIVLGCQYLHRNRVIHRDLK  
LGNLFLNEDLEV KIGDFGLATKVEYDGERKKTLCGTPNYIAPEVLSKKGHSFEVDVWSIG  
CIMYTLLVGKPPFETSCLKETYLR IKKNEYSIPKHINPVAASLIQKMLQTDPTARPTINELL  
NDEFFTSGYIPARLPITCLTIPPRFSIAPSSLDPSNRKPLTVLNKGLENPLPERPREKEEP  
VVRETGEVVDCHLS DMLQQLHSVNASKP SERGLVRQEEAEDPACIPIFWVSKWVDYSD  
KYGLGYQLCDNSVGVL FNDSTR LILYNDGDSLQYIERDGTESYLT VSSHPNSLMKKITLL  
KYFRNYMSEHLLKAGANITPREGDELARLPYLRTWFRTRSAILHLSNGSVQINFFQDHT  
KLILCPLMAAVTYIDEKRDFRTYRLSLLEEYGCCKELASRLRYARTMVDKLLSSRSASNR  
LKAS

SEQ ID No:24

MGCVQCKDKEATKLTEERDGS LNQSSGYRYGTDPTPQHYP SFGVTSIPNYNNFHAAG  
GQGLTVFGGVNSSSHTGTLRTRGGTGVT LFLVALYDYEARTEDDLSFHKG EK FQILNSST  
KKGGKEGPEPQEIRFAGRSDLLEGNHVVDCRLVEGSADTQWMSEPQRHIHGLPDVNG  
KRWYFGKLGRKDAERQLLSFGNPRGTFLIRESETTKGAYSLSIRDWDDMKGDHVKHYK  
IRKLDNGGYYITTRAQFETLQQLVQHYSERAAGLCCRLVVPCHKGMPRLTDLSVKT KD V  
WEIPRESLQLIKRLGNGQFGEVWMGTWNGNTKVAIKTLKPGTMSPE SFLEEAQIMKKLK

HDKLVQLYAVVSEEPYIVTEYMNKGSLLDFLKDGEGRALKLPNLVDMAAQVAAGMAYI  
ERMNYIHRDLRSANILVGNGLICKIADFGRLARLIEDNEYTARQGAKFPIKWTAPEAALYGR  
FTIKSDVWSFGILLTELVTKGRVPYPGMNNREVLEQVERGYRMPCPQDCPISLHELMIH  
CWKKDPEERPTFEYLQSFLEDYFTATEPQYQPGENL

SEQ ID No:25

MDAEG LALLLPVTLAALVDSWLREDCPGLNYAALVSGAGPSQAALWAKSPGVLGQP  
FFDAIFTQLNCQVSWFLPEGSKLVPVARVAEVRGPAHCLLLGERVALNTLARCSGIA  
AAAAVEAARGAGWTGHVAGTRKTTGFRLEKYGLLVGGAASHRYDLGGLVMVKDNH  
VVAAGGVEKAVRAARQAADFALKVEVECCSLQEAVQAAEAGADLVLLDNFKPEELHPT  
ATVLKAQFPSVAVEASGGITLDNLPQFCGPHIDVISMGMLTQAAPALDFSLKLFAKEVAP  
VPKIH

SEQ ID No:26

MSELEKAMVALIDVFHQYSGREGDKHKLKSELKELINNELSHFLEEIKEQEVVDKVMET  
LDNDGDGECDFQEFMAFVAMVTTACHEFFEHE

SEQ ID No:27

MWAEAGLPRAGGGSQPPFRTFSASDWGLTHLVVHEQTGEVYVGAVNRIYKLSGNLTL  
LRAHVTGPVEDNEKCYPPPSVQSCPHGLGSTDNVNKL LLLDYAANRLLACGSASQGIC  
QFLRLDDLFLKLGEPHHRKEHYLSSVQEAGSMAGVLIAGPPGQGQAKLFVGTPIDGKSE  
YFPTLSSRRLMANEEDADMFGFVYQDEFVSSQLKIPSDTLSKFPAFDIYYVYSFRSEQF  
VYYLTLQLDTQLTSPDAAGEHFFTSKIVRLCVD DPKFYSYVEFPIGCEQAGVEYRLVQD  
AYLSRPGRALAHQLGLAEDEDVLFVFAQGQKNRVKPPKESALCLFTLRAIKEKIKERIQ  
SCYRGEGKLSLPWLLNKELGCINSPLQIDDDFCGQDFNQPLGGTVTIEGTPLFVDKDDG  
LTAVAAAYDYRGRTVVFAGTRSGRIRKDL SNPGGRP ALAYESVVAQEGSPILRDLVLSPN  
HQYLYAMTEKQVTRVPVESCVQYTSCELCLGSRDPHCGWCVLHSICSRRDACERADE  
PQRFAADLLQCVQLTVQPRNVSVTMSQVPLVLQAWNVPDLSAGVNCSFEDFTESESVL  
EDGRIHCRSPSAREVAPITRGQGDQRVVKLYLKS KETGKKFASVDFVFYNCSVHQSC  
SCVNGSFPCHWCKYRHVCTHNVADCAFLEGRVNVSEDCPQILPSTQIYVPVGVVKPITL  
AARNLPQPQSGQRGYECLFHIPGSPARVTALRFNSSLQCCQNSSYSYEGNDVSDLPVN  
LSVVWNGNFVIDNPQNIQAHLYKCPALRESCGLCLKADPRFECGWCVAERRCSLRHHC  
AADTPASWMHARHGSSRCTDPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVR  
VGKVLCSPESEYISAEQIVCEIGDASSVRAHDALVEVCVRDCSPHYRALSPKRFTFVTP

TFYRVSPSRGPLSGGTWIGIEGSHLNAGSDVAVSVGGRPCSFSWRNSREIRCLTPPGQ  
 SPGSAPIIININRAQLTNPEVKYNYTEDPTILRIDPEWSINSGGTLLTVTGTNLATVREPRI  
 RAKYGGIERENGCLVYNDTTMVCRAPSVANPVRSPPELGERPDELGFVMDNVRSLVL  
 NSTSFLYYDPVLEPLSPTGLLELKPSSPLILKGRNLLPPAPGNSRLNYTVLIGSTPCTLT  
 VSETQLLCEAPNLTGQHKVTVRAGGFESPGLTQVYSDSLLTLPAIVGIGGGGGGLLLVI  
 VAVLIAYKRKSRDADRTLKRLQLQMDNLESRVALECKEAFELQTDIHELTDLDGAGIP  
 FLDYRTYAMRVLFPGIEDHPVLKEMEYQANVEKSLTLFGQLLTKKHFLLTFTIRLEAQRS  
 FSMRDRGNVASLIMTALQGEMEYATGVLKQLLSDLIEKNLESKNHPKLLLRRTESVAEK  
 MLTNWFTFLLYK

FLKECAGEPLFMLYCAIKQQMEKGPIDAITGEARYSLSEDKLIRQQIDYKTLTLNCVNPEN  
 ENAPEVPVKGLDCDTVTAKEKLLDAAYKGVYPYSQRPKAADMDLEWRQGRMARIILQD  
 EDVTTKIDNDWKRLNTLAHYQVTDGSSVALVPKQTSAYNISNSSTFTKSLSRYESMLRT  
 ASSPDSLRSRTPMITPDLESGTKLWHLVKNHDLHDQREGDRGSKMVSEIYLTRLLATKG  
 TLQKFVDDLFEFIFSTAHRGSALPLAIKYMFDLDEQADKHQIHDADVHTWKSNCPLR  
 FWVNVIKNPQFVFDIHKNSITDACLSVVAQTFMDSCSTSEHKLKGDSPSNKLLYAKDIPN  
 YKSWVERYYADIAKMPAISDQDMSAYLAEQSRLHLSQFNSMSALHEIYSYITKYKDEILA  
 ALEKDEQARRQRLRSKLEQVVDTMALSS

SEQ ID No:28

MAQGLEVALTDLQSSRNVRHHTEEITVDHLLVRRGQAFNLTYFRNRSFQPGLDNIIFV  
 VETEDAVYLDSEPQRQEYVMNDYGFIYQGSKNWIRPCPWNYGQFEDKIIDICLKLLDKS  
 LHFQTDPATDCALRGSPVYVSRVVCAMINSNDDNGVLNGNWSSENYTDGANPAEWTGS  
 VAILKQWNATGCQPVRYGQCWVFAAVMCTVMRCLGIPTRVITNFDSGHDTDGNIIDEY  
 YDNTGRILGNKKKDTIWNFHVWNECWMARKDLPPAYGGWQVLDATPQEMSNGVYCC  
 GPASVRAIKEGEVDLNYDTPFVFSMVNADCMSWLQGGKEQKLHQDTSSVGNFISTKS  
 IQSDERDDITENYKYEESLQERQVFLKALQKLKARSFHGSQRGAELQPSRPTSLSQDS  
 PRSLHTPSLRPSDVVQVSLKFKLLDPPNMGQDICFVLLALNMSSQFKDLKVNLSAQSL  
 HDGSPLSPFWQDTAFITLSPKEAKTYPCKISYSQYSQYLSTDKLIRISALGEEKSSPEKIL  
 VNKIITLSYPSITINVLGAAVVNQPLSIQVIFSNPLSEQVEDCVLTVEGSGLFKKQKQVFLG  
 VLKPQHQASIILETVPFKSGQRQIQANMRSNKFKDIDYGRNVYVDFAL

SEQ ID No:29

MGTSALWALWLLLALCWAPRESGATGTGRKAKCEPSQFQCTNGRCITLLWKCDGDED  
 CVDGSDEKNCVKKTCAESDFVCNNGQCVPSRWKCDGDPDCEDGSDESPEQCHMRT

CRIHEISCGAHSTQCIPVSWRCDGENDCDSGEDEENCGNITCSPDEFTCSSSGRCISRNF  
VCNGQDDCSDGSDELDCAPPTCGAHEFQCSTSSCIPISWVCDDDDADCSDQSDLESLEQ  
CGRQPVIHTKCPASEIQCGSGECIHKKWRCDGDPDCKDGSDEVNCPSTRCPDQFEC  
EDGSCIHGSRQCNGIRDCVDGSDEVNCKNVNQCLGPGKFKCRSGECIDISKVCNQEQ  
DCRDWSDEPLKECHINECLVNNGGCSHICKDLVIGYECDAAGFELIDRKTCGDIDECQ  
NPGICSQICINLKGGYKCECSRQYQMDLATGVCKAVGKEPSLIFTNRRDIRKIGLERKEYI  
QLVEQLRNTVALDADIAAQKLFWADLSQKAIFSASIDDKVGRHVKMIDNVYNPAAIAVDW  
VYKTIYWTDAAASKTISVATLDGTRKFLFNSDLREPASIAVDPLSGFVYWSWGWGEPKIE  
KAGMNGFDRRPLVTADIQWPNGITLDLIKSRLYWLD SKLHMLSSVDLNGQDRRIVLKS  
EFLAHPLALTIFEDRVYWIDGENEAVYGANKFTGSELATLVNNLNDAQDIIVYHELVQPS  
GKNWCEEDMENGGEYLCLPAPQINDHSPKYTCSCPSGYNVEENGRDCQSTATTVTY  
SETKDTNTTEISATSGLVPGGINVTTAVSEVSVPPKGTSAAWAILPLLLLVMMAVGGGYLM  
WRNWQHKNMKSMNFDNPVYLKTTEEDLSIDIGRHSASVGHTYPAISVVSTDDDLA

SEQ ID No:30

MSAAEAGGVFHRARGRTLDAFP AEKESEWKGP FYFILGADPQFGLIKAWSTGDCDNG  
GDEWEQEIRLTEQAVQAINELNPKPKFFVLCGDLIHAMPGKPWRTEQTEDLKRVLRAVD  
RAIPLVLVSGNHDIGNTPTAETVEEFCRTWGDDYFSFWVGGVFLVLNSQFYENPSKCP  
SLKQAQDQWLDEQLSIARQRHCQHAIVFQHIPLFLESIDEDDDYFNL SKSTRKELADKF  
IHAGVRVVFSGHYHRNAGGTYQNLDMVVSSAIGCQLGRDPHGLRVVVVTAEKIVHRY  
SLDELSEKGIEDDLMDLIKKK

SEQ ID No:31

MESYDVIANQPVIDNGSGVIKAGFAGDQIPKYCFPNYVGRPKHVRVMAGALEGDIFIG  
PKAEHRGLLSIRYPMEHGIVKDWN DMERIWQYVYSKDQLQTFSEEHPVLLTEAPLNP  
RKNRERAAEVFFETFNVPALFISMQAVLSLYATGRTTGVLDSGDGVTHAVPIYEGFAM  
PHSIMRIDIAGRDSRFLRLYL RKEGYDFHSSSEFEIVKAIKERACYLSINPQKDETLETE  
KAQYYLPDGSTIEIGPSRFRAPPELLFRPDLIGEES EGIHEVLVFAIQKSDMDLRRTLFSNIV  
LSGGSTLFKGFGRLLSEVKKLAPKDVKIRISAPQERLYSTWIGGSILASLDTFKKMWVS  
KKEYEEDGARSIRKTF

SEQ ID No:32

MSNPRSLEEEKYDMSGARLALILCVTKAREGSEEDLDALEHMFRQLRFESTMKRDPTA  
EQFQEELEKFQQAIDSREDPVSCAFVVLMAHGREGFLKGEDGEMVKLENLFEALNNKN

CQALRAKPKVYIIQACRGEQRDPGETVGGDEIVMVIKDSPQTIPTYTDALHVYSTVEGYI  
AYRHDQKGSCFIQTLVDVFTKRKGHILELLTEVTRRMAEAEVLQEGKARKTNPEIQSTLR  
KRLLYLQ

SEQ ID No:33

MMRQAPTARKTTTTRRPKPTRPASTGVAGASSSLGPSGSASAGELSSSEPSTPAQTPLA  
APIIPTPVLTSPGAVPPLSPSPSKEEEGLRAQVRDLEEKLETLRKRAEDKAKLKELEKHKI  
QLEQVQEWKSKMQEQQADLQRRLEKEARKEAKEALEAKERYMEEMADTADAIEMATLD  
KEMAEERAESLQQEVEALKERVDELTTDLEILKAEIEEKGS DGAASSYQLKQLEEQNAR  
LKDALVRMRDLSSEKQEHVKLQKLMEKKNQELEVVRQQRERLQEELSQAESTIDELK  
EQVDAALGAEEMVEMLTDRNLNLEEKVRELRETVGDLEAMNEMNDELQENARETELEL  
REQLDMAGARVREAQKRVEAAQETVADYQQTIKKYRQLTAHLQDVNREL TNQQEASV  
ERQQQPPPETFDFKIKFAETKAHAKAIEMELRQMEVAQANRHMSLLTAFMPDSFLRPG  
GDHDCVLVLLLMPRLICKAELIRKQAQEKFELSENC SERPGLRGAAGEQLSFAAGLVYS  
LSLLQATLHRYEHALSQCSVDVYKKVGS LYPEMSAHERSLDFLIELLHKDQLDET VNVE  
PLTKAIKYYQHLYSIHLAEQPEDCTMQLADHIKFTQSALDCMSVEVGRLRAFLQGGQEA  
TDIALLLRDLETSCSDIRQFCKIRRRMPGTDAPGIPAALAFGPQVSDTLLDCRKHLTWV  
VAVLQEVAIAAQAQLIAPLAENEGLLVAALEELAFKASEQIYGTPSSSPYECLRQSCNILIS  
TMNKLATAMQEGEYDAERPPSKPPPVELRAAALRAEITDAEGLGLKLEDRETVIKELKK  
SLKIKGEELSEANVRLSLEKKLDSAAKDADERIEKVQTRLEETQALLRKKEKEFEETMD  
ALQADIDQLEAEKAELKQRLNSQSKRTIEGLRGPPPSGIATLVSGIAGEEQQRGAI PGQA  
PGSVPGPGLVKDSPLLLQQISAMRLHISQLQHENSILKGAQMKASLASLPPLHVAKLSHE  
GPGSELPAGALYRKTSQ LLETNLQLSTHTHVVDITRTSPA AKSPSAQLMEQVAQLKSLS  
DTVEKLDKDEVLKETVSQRPGATVPTDFATFPSSAFLRAKEEQQDDTVYMGKVTFSCAA  
GFGQRHRLVLTQEQLHQLHSRLIS

SEQ ID No:34

MAGLTDLQRLQARVEELERWVYGPGGARGSRKVADGLVKVQVALGNISSKRERVKILY  
KKIEDLIKLYLDPEYIDRIAIPDASKLQFILAE EQFILSQVALLEQVNALVPMLDSAHIKAVPE  
HAARLQRLAQIHQQAPWGVGVRDEAGSLVEDVGFAQFLSVLHFGPTGPVCGNH

SEQ ID No:35

MPLYEGLGSGGEKTAVVIDLGEAFTKCGFAGETGPRCIIPSVIKRAGMPKPV RVVQYNIN  
TEELYSYLKEFIHILYFRHLLVNPRDRRVVIESVLCPSHFRET LTRVLFKYFEVPSVLLAP

SHLMALLTLGINSAMVLDCGYRESLVLPISFLSASHLCRIPVLNCWGALPLGGKALHKEL  
ETQLEQCTVDTSVAKEQSLPSVMGSPVEGVLEDIKARTCFVSDLKRGLKIQAAKFNIDG  
NNERPSPPPNVDYPLDGEKILHILGSIRDSVVEILFEQDNEEQSVATLILDSLIQCPIDTRK  
QLAENLVVIGGTSMPLPGFLHRLAEIRYLVEKPKYKKALGKTFRHTPPAKANCVAWLG  
GAIFGALQDILGSRSVSKEYYNQTGRIPDWCSLNNPPLEMMFDVGKTQPPLMKRAFST  
EK

SEQ ID No:36

MLPDFPSPSTWAPGLLLPSGPALLSPSVLQDSLGLRSEQPHPICSFQDDFQEFEMIDD  
NEEEDDEDEEEEEEEEEEGDGEGQEGGDPGSEAPAPGPLIPSPSVEEPHKHRPTTLRLT  
TLGAQDSLNNNGGFDLVRPASWQETALCSPAPEALRELPGPLPATDTGPGGAQSPVR  
PGCDCEGNRPAEPPAPGGTSPSSDPGIEADLRSSSGGRGRRSSQELSSPGSDSED  
AGGARLGRMISSISETELELSSDGGSSSSGRSSHLTNSIEEASSPASEPEPPREPPRRP  
AFLPVGPDNTNSEYESGSESEPDLSADSPWLLSNLVSRMISEGSSPIRCPGQCLSPA  
PRPPGEPVSPAGGAAQDSQDPEAAAGPGGVELVDMETLCAPPPAPAAPRPGPAQP  
GPCFLSNPTRDTITPLWAAPGRAARPGRACSAACSEEEDEEDDEEEEDAEDSAGSPG  
GRGTGPSAPRDASLVYDAVKYTLVVDEHTQLELVSLRRCAGLGHDSEEDSGGEASEEE  
AGAALLGGGQVSGDTPDSDPLTFSKKFLNVFNSTSRSSSTESFGLFSCLVNGEERE  
QTHRAVFRFIPRHPDELELDVDDPVLVEAEEDDFWFRGFNMRTGERGVFPFYAHAVP  
GPAKDLLGSKRSPCWVERFDVQFLGSVEVPCHQGNLCAAMQKIATARKLTVHLRPP  
ASCDLEISLRGVKLSLSGGGPEFQRCSHFFQMKNISFCGCHPRNSCYFGFITKHPLLSR  
FACHVFVSQESMRPVAQSVGRAFLEYQEHLAYACPTEDIYLE

SEQ ID No:37

MAERESGGLGGGAASPPAASPFLGLHIASPPNFRLTHDISLEEFEDDLSEITDECGISL  
QCKDTLSLRPPRAGLLSAGGGGAGSRLQAEMLQMDLIDATGDTPGAEDDEEDDDEER  
AARRPGAGPPKAESGQEPASRGQGQSQGQSQGPGSGDTPRKRPTTLNLFQVPRS  
QDTLNNNSLGKKHSWQDRVSRSSSPLKTGEQTPPHEHICLSDELPPQSGPAPTTDRGT  
STDSPCRRSTATQMAPPGGPPAAPPGGRGHSHRDRIHYQADVRLATEEIIYLPVQRP  
PDAAEPTSAFLPPTESRMSVSSDPDPAAYPSTAGRPHPSISEEEEGFDCLSSPERAEP  
GGGWRGSLGEPPPPPRASLSSDTSALSYDSVKYTLVVDEHAQLELVSLRPCFGDYSDE  
SDSATVYDNCASVSSPYESAIGEEYEEAPRPQPPACLSDESTPDEPDVHFSKKFLNVF  
MSGRSRSSSAESFGLFSCIINGEEQEQTTHRAIFRFVPRHEDELELEVDDPLLVELQAED  
YWYEAYNMRTGARGVFPAYYAIEVTKEPEHMAALAKNSDWVDQFRVKFLGSVQVPYH

KGNDVLCAAMQKIATTRRLTVHFNPPSSCVLEISVRGVKIGVKADDSQEAKGNKCSHFF  
QLKNISFCGYHPKNNKYFGFITKHPADHRFACHVVFVSEDSTKALAESVGRAFQQFYKQF  
VEYTCPTEDIYLE

SEQ ID No:38

MSRSKRDNNFYVSVEIGDSTFTVLKRYQNLKPIGSGAQQGIVCAAYDAILERNVAIKKLSRP  
FQNQTHAKRAYRELVLKCVNHKNIIIGLLNVFTPQKSLEEFQDVYIVMELMDANLCQVIQ  
MELDHERMSYLLYQMLCGIKHLHSAGIIHRDLKPSNIVVKSDCTLKILDFGLARTAGTSF  
MMTPYVVTRYRAPEVILGMGYKENVDLWSVGCIMGEMVCHKILFPGRDYIDQWNKVI  
EQLGTPCPEFMKKLQPTVRTYVENRPKYAGYSFEKLFPDVLFPADSEHNKLKASQARD  
LLSKMLVIDASKRISVDEALQHPYINVWYDPSEAEAPPPKIPDKQLDEREHTIEEWKELIY  
KEVMDLEERTKNGVIRGQPSPLAQVQQ

SEQ ID No:39

MADLAECNIKVMCRFRPLNESEVNRGDKYIAKFQGEDTVVIASKPYAFDRVFQSSTSQE  
QVYNDCAKKIVKDVLEGYNGTIFAYGQTSSGKTHTMEGKLHDPEGMGIIIPRIVQDIFNYI  
YSMDENLEFHIKVSYFEIYLDKIRDLLDVSKTNLSVHEDKNRVPYVKGCTERFVCSDEV  
MDTIDEGKSNRHVAVTNMNEHSSRSHSIFLINVKQENTQTEQKLSGKLYLVDLAGSEKV  
SKTGAEGAVLDEAKNINKSLSALGNVISALAEGSTYVPYRDSKMTRILQDSLGGNCRTTI  
VICCSPSSYNESETKSTLLFGQRAKTIKNTVCVNVELTAEQWKKKYEKEKEKNKILRNTI  
QWLENELNRWRNGETVPIDEQFDKEKANLEAFTVDKDITLTNDKPATAIGVIGNFTDAE  
RRKCEEEIAKLYKQLDDKDEEINQQSQLVEKLKTQMLDQEELLASTRRDQDNMQAELN  
RLQAENDASKEEVKEVLQALEELAVNYDQKSQEVEDKTKEYELLSDELNQKSATLASID  
AELQKLKEMTNHQKKRAAEMMASLLKDLAEIGIAVGNNNDVKQPEGTGMIDEEFTVARLY  
ISKMKSEVKTMVKRCKQLESTQTESNKKMEENEKELAACQLRISQHEAKIKSLTEYLQN  
VEQKKRQLEESVDALSEELVQLRAQEKVHEMEKEHLNKVQTANEVKQAVEQQIQSHRE  
THQKQISSLRDEVEAKAKLITDLQDQNNQMMLEQERLRVEHEKLNKATDQEKSRKLHELT  
VMQDRREQARQDLKGLEETVAKELQTLHNLRKLFVQDLATRVKKSAEIDSDDTGGSA  
QKQKISFLENNLEQLTKVHKQLVRDNADLRCELPKLEKRLRATAERVKALESALKEAKE  
NASRDRKRYQQEVDRIKEAVRSKNMARRGHSAAQIAKPIRPGQHPAASPTHPSAIRGGG  
AFVQNSQPVAVRGGGGGKQV

SEQ ID No:40



MSTMVYIKEDKLEKLTQDEIISKTKQVIQGLEALKNEHNSILQSLLETCLKLKKDDSNLV  
 EEKSNMIRKSLEMLELGLSEAQVMMALS NHLNAVESEKQKLRAQVRRLCQENQWLRD  
 ELANTQQKLQKSEQSVAQLEEEKKHLEFMNQLKKYDDDISPSEDKDT DSTKEPLDDLFP  
 NDEDDPGQGIQQQHSSAAAAAQQGGYEIPARLRTLHNLVIQYASQGRYEVAVPLCKQA  
 LEDLEKTSGHDHPDVATMLNILALVYRDQNKYKDAANLLNDALAIREKTLGKDHPAVAAT  
 LNNLAVLYGKRGKYKEAEPLCKRALEIREKVLGKDHPDVAKQLNNLALLCQNQKGKYEYV  
 EYYYQRALEIYQTKLGPDDPNVAKTKNNLASCYLKQKGKFKQAETLYKEILTRAHEREFG  
 SVDDENKPIWMHAEERECKGKQKDGT SFGEYGGWYKACKVDSPTVT TTTLKNLGALY  
 RRQKGFEAAETLEEAAMRSRKQGLDNVHKQRVAEVLNDPENMEKRRSRESLNVDVVK  
 YESGPDGGEEVSM SVEWNGGVSGRASFCGKRQQQQWPGRHR

SEQ ID No:41

MADPAEC SIKVMCRFRPLNEAEILRGDKFIPKFKGDET VVIGQGKPYVFDRLPPNTTQE  
 QVYNACAKQIVKDVLEGYNGTIFAYGQTSSGKTH TMEGKLHDPQLMGIIPRIAH DIFDHIY  
 SMDENLEFHIKVS YFEIYLDKIRDLLDVSKTNLAVHEDKNRVPYVKGCTERFVSSPEEVM  
 DVIDEGKANRHVAVTNMNEHSSRSHSIFLINIKQENVETEK KLSGKLYLVDLAGSEK VSK  
 TGAEGAVLDEAKNINKSLSALGNVISALAEGTKTHVPYRDSKMTRILQDSLGGNCRTTIVI  
 CCSPSVFNEAETKSTLMFGQRAKTIKNTVSVNLELTAE EWKKKYEKEKEKNKTLKNVIQ  
 HLEMELNRWRNGEAVPEDEQISAKDQKNLEPCDNTPIIDNIAPV VAGISTEEKEYDEEI  
 SSLYRQLDDKDDEINQQSQLAEK LKQQMLDQDELLASTRRDYEKIQEELTRLQIENEAA  
 KDEVKEVLQALEELAVNYDQKSQEVEDKTRANEQLTDELAQKTTT LTTTQRELSQLQEL  
 SNHQKKRATEILNLLLKDLGEIGGIIGTNDVKT LADVNGVIEEFTMARLYISKMKSEVKSL  
 VNRSKQLESAQMDSNRKMNASERELAACQL LISQHEAKIKSLTDYMQNMEQKRRQLEE  
 SQDSLSEELAKLRAQEK MHEVSFQDKEKEHLTRLQDAEEMKKALEQQMESHREAHQK  
 QLSRLRDEIEEKQKIIDEIRD LNQKLQLEQEK LSSDYNK LKIEDQEREMKLEKLLLLNDKR  
 EQARED LKGLEETVSRELQTLHNLRLKLFVQDLTTRVKKSVELDNDDGGGSAAQKQKISF  
 LENNLEQLTKVHKQLVRDNADLRCELPKLEKRLRATAERVKALESALKEAKENAMRDRK  
 RYQQEVDRIKEAVRAKNMARRAHSAQIAKPIRPGHYPASSPTAVHAIRGGGGSSSNST  
 HYQK

SEQ ID No:42

MGPASPAARGLSRRPGQPPLPLLLPLLLLLLRAQPAIGSLAGGSPGAAEAPGSAQVAGL  
 CGRLTLHRDLRTGRWEPDPQRSRRCLRDPQRVLEYCRQMYPELQIARVEQATQAIPM  
 ERWCGGSRSGSCAHPHHQVVPFRCLPGEFVSEALLVPEGCRFLHQERMDQCESSTR

RHQEAQEACSSQGLILHGSGMLLPCGSDRFRGVEYVCCPPPGTPDPSTAVGDPSTR  
 SWPPGSRVEGADEEEEEESFPQPVDDYFVEPPQAEEEEETVPPSSHTLAVVGKVTPT  
 PRPTDGVDIYFGMPGEISEHEGFLRAKMDLEERRMRQINEVMREWAMADNQSKNLPK  
 ADRQALNEHFQSILQTL EEQVSGERQRLVETHATRVIALINDQRRAALEGFLAALQADPP  
 QAERVLLALRRYLRAEQKEQRHTLRHYQHVAAVDPEKAQQMRQVHHTLQVIEERVN  
 QSLGLLDQNPFLAQELRPQIQELLHSEHLGPSELEAPAPGGSSSEDKGGLQPPDSKDDT  
 PMTLPKGSTEQDAASPEKEKMNPLEQYERKVNASVPRGFPFHSSEIQRDELAPAGTGV  
 SREAVSGLLIMGAGGGSLIVLSMLLLRRKKPYGAISHGVVEVDPMLTLEEQQRELQRH  
 GYENPTYRFLEERP

SEQ ID No:43

AGARRRRGRGGEEAPLLPGLAAAEPPEARPDGLAEPAVRGRRVGSGRGTMSAKVRLK  
 KLEQLLLDGPWRNESALSVETLLDVLVCLYTECSHSALRRDKYVAEFLEWAKPFTQLVK  
 EMQLHREDFEIIKVI GRGAFGEVAVVKMKNTERIYAMKILNKWEMLKRAETACFREERD  
 VLVNGDCQWITALHYAFQDENHLYLVMDYYVGGDLLTLLSKFEDKLPEDMARFYIGEMV  
 LAIDSIHQLHYVHRDIKPDNVLLDVNGHIRLADFGSCLKMNDGTVQSSVAVGTPDYISP  
 EILQAMEDGMGKYGPECDWWSLGVCMYEMLYGETPFYAESLVETYGKIMNHEERFQF  
 PSHVTDVSEEAKDLIQRILCSRRRLGQNGIEDFKKHAFEGNLNWNIRNLEAPYIPDVS  
 SPSDTSNFDVDDDLRNTILPPGSHTGFSGHLHPFIGFTFTTESCFSDRGSLKSIMQSN  
 TLTKDEDVQRDLEHSLQMEAYERRIRRLQEKELELSRKLQESTQTVQSLHGSSRALSNS  
 NRDKEIKKLNEEIERLKNKIADSNRLERQLEDTVLRQEREDSTQRLRGLEKQHRVVRQ  
 EKEELHKQLVEASERLKSQAKELKDAHQQRKLALQEFSELNERMAELRAQKQKVSRL  
 RDKEEEME VATQKVDAMRQEMRRAEKL RKELEAQLDDAVAEASKERKLREHSENFCK  
 QMESELEALKVKQGGRGAGATLEHQQEISKIKSELEKKVLFYEEELVRREASHVLEVKN  
 VKKEVHDSESHQLALQKEILMLKDKLEKSKRERHNEMEEAVGTIKDKYERERAMLFDEN  
 KKL  
 TAENEKLCSFVDKLT AQNRQLEDELQDLAAKESVAHWEAQIAEIIQWVSDEKDARGYL  
 QALASKMTEELEALRSSSLGSRTLDPLWKVRRSQKLDMSARLELQSALEAEIRAKQLVQ  
 EELRKVKDANLTLESKLDSEAKNRELLEEMEILKKKMEEKFRADTGLKLPDFQDSIFEY  
 FNTAPLAHDLTFR TSSASEQETQAPKPEASPSMSVAASEQQEDMARPPQRPSAVPLPT  
 TQALALAGPKPKAHQFSIKSFSSPTQCSHCTSLMVGLIRQGYACEVCSFACHVSCKDG  
 APQVCPIPPEQSKRPLGVDVQRGIGTAYKGHV KVPKPTGVKKGWQRAYAVVCDCKLFL  
 YDLPEGKSTQPGVIASQVLDLRDDEFSVSSVLASDVIHATRRDIPCIFRVTASLLGAPSKT  
 SLLILTENENEKKKWVGILEGLQSILHKNRLRNQVVHVPLEAYDSSLPLIKAILTAAIVDA

DRIAVGLEEGLYVIEVTRDVIVRAADCKKVHQIELAPREKIVILLCGRNHHVHLYPWSSLD  
GAEGSFDIKLPETKGCQLMATATLKRNSGTCLFVAVKRLILCYEIQRTPFHRKFNEIVAP  
GSVQCLAVLRDRLCVGYPSGFCLLSIQGDGQPLNLVNPNDPSLAFLSQQSFDALCAVEL  
ESEEYLLCFSHMGLYVDPQGRRARAQELMWPAAPVACSCSPHTVTVYSEYGVDVFDV  
RTMEWVQTIGLRRIRPLNSEGTLNLLNCEPPRLIYFKSKFSGAVLNVPDTSDNSKKQML  
RTRSKRRFVFKVPEEERLQQRREMLRDPELRSKMISNPTNFNHVAHMGP GDGMQVLM  
DLPLSAVPPSQEERPGPAPTNLARQPPSRNKPYSISWPSSGGSEPSVTVPLRMSDPDQ  
DFDKEPDSDSTKHSTPSNSSNPSGPPSPNSPHRSQPLPLEGLEQPACDT

SEQ ID No:44

MPVAVMAESAFSFKLLDQCENQELEAPGGIATPPVYGQLLALYLLHNDMNNARYLWK  
RIPPAIKSANSELGGIWSVGQRIWQRDFPGIYTTINAHQWSETVQPIMEALRDATRRRAF  
ALVSQAYTSIIADDFAAFVGLPVEEAVKGILEQGWQADSTTRMVLPRKPVAGALDVSN  
KFIPLSEPAPVPPIPNEQQLARLTDYVAFLEN

SEQ ID No:45

MAAAVRQDLAQLMNSSGSHKDLAGKYRQILEKAIQLSGAEQLEALKAFVEAMVNENV  
LVISRQLLTDFCTHLPNLPDSTAKEIYHFTLEKIQPRVISFEEQVASIRQH LASIYEKEEDW  
RNAAQVLVGIPLETGQXXQYNVDYKLETY LKIARLYLEDDDPVQAEAYINRASLLQNEST  
NEQLQIHVKVCYARVLDYRRKFIEAAQRYNELSYKTIVHESERLEALKHALHCTILASAG  
QQRSRMLATLFKDERCQQLAAYGILEKMYLDRIIRGNQLQEFAAMLMPHQKATTADGS  
SILDRAVIEHNLLSASKLYNNITFEELGALLEIPA AKA EKIASQMITEGRMNGFIDQIDGIVH  
FETREALPTWDKQIQSLCFQVNNLLEKISQTAPEWTAQAMEAQMAQ

SEQ ID No:46

MSAEVKVTGQNQEQLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESD  
FASTFRLLTVFAYGTYADYLAEARNLPPLTEAQKNKL RHLSVVT LAAKV KCIPYAVLLEAL  
ALRNVRQLEDLVIEAVYADVLRGSLDQRNQRLEV DYSIGRDIQRQDLSAIARTLQEWCV  
GCEVVLSGIEEQVSRANQHKEQQLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQH  
LTELREPAPGTNQRQPSKKASKGKGLRGS AKIWSKSN

SEQ ID No:47

MASALEQFVNSVRQLSAQGQMTQLCELINKSGELLAKNLSHLDTVLGALDVQEHS LGVL  
AVLFVKFSMPSPVDFETLFSQVQLFISTCNGEHIRYATDTFAGLCHQLTNALVERKQPLR

GIGILKQAIDKMQMNTNQLTSIHADLCQLCLLAKCFKPALPYLDVDMMDICKENGAYDAK  
HFLCYYYYGGMIYTGLKNFERALYFYEQAITTPAMAVSHIMLESYKKYILVSLILLGKVQQ  
LPKYTSQIVGRFIKPLSNAYHELAQVYSTNNPSELRLNVNKHSETFTRDNNMGLVKQCL  
SSLYKKNIQRLTKTFLTLSLQDMASRVQLSGPQEAKEYVLHMIEDGEIFASINQKDGMVS  
FHDNPEKYNNPAMLHNIDQEMLKCIELDERLKAMDQEITVNPQFVQKSMGSQEDDSGN  
KPSSYS

SEQ ID No:48

MAASGSGMAQKTWELANNMQEAQSIDEIYKYDKKQQQEILAAANLGTKDHHYFKYCKIS  
ALALLKMVMHARSGGNLEVMGLMLGKVDGETMIIMDSFALPVEGTETRVNAQAAAYEY  
MAAYIENAKQVGRLENAIGWYHSHPGYGCWLSGIDVSTQMLNQQFQEPFVAVVIDPTR  
TISAGKVNLGAFRTYTPKGYKPPDEGPSEYQTIPLNKIEDFGVHCKQYYALEVSYFKSSLD  
RKLELLWNKYWVNTLSSSSLLTNADYTTGQVFDLSEKLEQSEAQLGRGSFMLGLETH  
DRKSEDKLAKATRDSCKTIEAIHGLMSQVIKDKLFNQINIS

SEQ ID No:49

MACGVTGSVSVALHPLVILNISDHWIRMRSQEGRPVQVIGALIGKQEGRNIEVMNSFELL  
SHTVEEKIIDKEYYYTKEEQFKQVFKELEFLGWYTTGGPPDPSDIHVHKQVCEIIESPLF  
LKLNPMTKHTDLPVSVFESVIDIINGEATMLFAELTYTLATEEAERIGVDHVARMTATGSG  
ENSTVAEHLIAQHSAILMLHSRVKLILEYVKASEAGEVPFNHEILREAYALCHCLPVLSTD  
KFKTDFYDQCNDVGLMAYLGTITKTCNTMNQFVNKFNVLYDRQGIGRRMRGLFF

SEQ ID No:50

MAGEQKPSSNLLEQFILLAKGTSGSALTALISQVLEAPGVYVFGELLELANVQELAEGAN  
AAYLQLLNLFAYGTYPDYIANKESLPELSTAQQNKLKHLTIVSLASRMKCIPIYSVLLKDLE  
MRNLRELEDLIEAVYTDIIQGKLDQRNQLLEVDFCIGRDIRKKDINNIVKTLHEWCDGCE  
AVLLGIEQQVLRANQYKENHNRTQQQVEAEVTNIKKTLKATASSSAQEMEQQLAEREC  
PPHAEQRQPTKKMSKVGLVSSRH

SEQ ID No:51

MSNLSKGTGSRKDTKMRIRAFPMTMDEKYVNSIWDLLKNAIQEIQRKNNSGLSFEELYR  
NAYTMVLHKHGEKLYTGLREVVTETHLINKVREDVLNSLNNNQLTLNQAWNDHQTAMV  
MIRDILMYMDRVYVQQNNVENVYNLGLIIFRDQVVRYGCIRDHLRQTLLDMIARERKGEV  
VDRGAIRNACQMLMILGLEGRSVYEEDFEAPFLEMSAEFFQMESQKFLAENSASVYIKK

VEARINEEIERVMHCLDKSTEEPIVKVVERELISKHMKTIVEMENSGLVHMLKNGKTEDL  
 GCMYKLFSRVPNGLKTMCECMSSYLREQGKALVSEEGEGKNPVDYIQGLLDLKSFRDR  
 FLLESFNNDRLFQKQTIAGDFEYFLNLNSRSPEYLSLFIDDKLKKGVKGLTEQEVETILDKA  
 MVLFRFMQEKDVFERYKQHLARRLLTNKSVSDDSEKNMISKLKTECGCQFTSKLEGM  
 FRDMSISNTTMDEFQRHLQATGVSLGGVDLTVRVLTGTYWPTQSATPKCNIPPAPRHA  
 FEIFRRFYLAHSGRQLTLQHMHMGSAADLNATFYGPVKKEDGSEVGVGGAQVTGSNTRK  
 HILQVSTFQMTILMLFNNREKYTFEEIQQETDIPERELVRALQSLACGKPTQRVLTKEPK  
 SKEIENGHIFTVNDQFTSKLHRVKIQTVAAKQGESDPERKETRQKVDDDRKHEIEAAIVRI  
 MKSRKKMQHNVLVAEVTQQLKARFLPSPVVIKKRIEGLIEREYLARTPEDRKVYTYVA

SEQ ID No:52

MSQFKRQRINPLPGGRNFSGTASTSLLGPPPGLLTPPVATELSQNARHLQGGEKQRVF  
 TGIVTSLHDYFGVVDEEVFFQLSVVKGRLPQLGEKVLVKAAYNPGQAVPWNNAVKVQTL  
 SNQPLLKSPAPPLHVAALGQKQGILGAQPQLIFQPHRIPPLFPQKPLSLFQTSHTLHLS  
 HLNRFPARGPHGRLDQGRSDDYDSKKRKQRAGGEPWGAKKPRHDLPPYRVHLTPYT  
 VDSPICDFLELQRRYRSLVPSDFLSVHLSWLSAFPLSQPFSLHHPSSRIQVSSEKEAAPD  
 AGAEPITADSDPAYSSKVLSSPGLEELYRCCMLFVDDMAEPRETPEHPLKQIKFLLGR  
 KEEEAVLVGGGEWSPSLDGLDPQADPQVLVRTAIRCAQAQTGIDLSGCTKWWRFAEFQ  
 YLQPGPPRRLQTVVVYLPDVWTIMPTLEEWEALCQQKAAEAAPPTQEAQGETEPTQA  
 PDALEQAADTSRRNAETPEATTQQETDLDPEAPPPPLEPAVIARPGCVNLSLHGIVED  
 RRPKERISFEAGVMVLAELFLEMLQRDFGYRVYKMLLSLPEKVVSPPPEPEKEEAAKEEA  
 TKEEEAIKEEVVKEPKDEAQNEGPATESEAPLKEDGLLPKPLSSGGEEEEKPRGEASED  
 LCEMALDPELLLLLRDDGEEEFAGAKLEDSEVRSVASNQSEMEFSSLQDMPKELDPSAV  
 LPLDCLLAFVFFDANWCGYLHRRDLERILLTLGIRLSAEQAKQLVSRVVTQNICQYRSLQ  
 YSRQEGLDGGLPEEVLFGNLDLLPPP GKSTKPGAAPTEHKALVSHNGSLINVGSLLQRA  
 EQQDSGRLYLENKIHTLELKLEESHNRFSATEVTNKTAAEMQELRVRLAEAEETARTA  
 ERQKSQQLRLLQELRRRLTPQLEIQRVVEKADSWVEKEEPAPSN

SEQ ID No:53

MLGKDYMLAILVNCDDDLWGDHSLEVEAGLPPGWRKIHDAAAGTYYWHVPSGSTQWQ  
 RPTWELGDAEDPGTGTEGIWGLRPPKGRSFSLESSLDRSNSLSWYGGESYIQSMEP  
 GAKCFAVRSLGWVEVPEEDLAPGKSSIAVNNCIQQLAQTRSRSQPPDGAWGEGQNML  
 MILKKDAMSLVNPLDHSLIHCQPLVHIRVWGVGSSKGRDRDFAFVASDKDSCMLKCHV  
 FRCDVPAKAIASALHGLCAQILSERVEVSGDASCCSPDPISPEDLPRQVELLDVAVSQAA

QKYEALYMGTLPTVKAMGMDVLNEAIGTLTARGDRNAWVPTMLSVSDSLMTAHPQAE  
ASTEELPLWQCPVRLVTFIGVGRDPHTFGLIADLGRQSFQCAAFWCQPHAGGLSEAVQ  
AACMVQYQKCLVASAARGKAWGAQARARLRKRTSSMDSPGGPLPLPLKGGVGA  
GATPRKRGVFSFLDAFRLKPSLLHMP

SEQ ID No:54

MDTSRLGVLLSLPVLLQLATGGSSPRSGVLLRGCPHCHCEPDGRMLLRVDCSDLGLS  
ELPSNLSVFTSYLDLSMNNISQLLPNPLPSLRFLEELRLAGNALTYIPKGAFTGLYSLKVL  
MLQNNQLRHVPTEALQNLRSLQSLRLDANHISYVPPSCFSGLHSLRHLWLDDNALTEIP  
VQAFRSLSALQAMTLALNKIHHIPDYAFGNLSSLVVHLHNNRIHSLGKKCFDGLHSLET  
LDLNYNNLDEFPTAIRTLNLKELGFHSNNIRSIPEKAFVGNPSLITIHFYDNPIQFVGRSA  
FQHLPELRTLTLNGASQITEFPDLTGATANLESLLTGAQISSLPQTVCNQLPNLQVLDLSY  
NLLEDLPFSFVCQKLQKIDLRHNEIYEIKVDTFQQLSLRSLNLAWNIAIHPNAFSTLPS  
LIKLDLSSNLLSSFPITGLHGLTHLKLGTGNHALQSLISSENFPELKVIEMPYAYQCCAFGV  
CENAYKISNQWNKGDNSSMDDLHKKDAGMFAQQDERDLEDFLDFFEDLKALHSVQC  
SPSPGPFKPCHELLDGWLIRIGVWTIAVLALTCNALVTSTVFRSPLYISPIKLLIGVIAAVN  
MLTGVSSAVLAGVDAFTFGSFARHGAWWENGVGCHVIGFLSIFASESSVFLTLAALER  
GFSVKYSAKFETKAPFSSLKVIILLCALLALTMAAVPLLGGSKYGASPLCLPLPFGEPSTM  
GYMVALILLNSLCFLMMTIAYTKLYCNLDKGDLENIWDCSMVKHIALLLFTNCILNCPVAF  
LSFSSLINLTFISPEVIKIFILLVVVPLPACLNPLLYILFNPHFKEDLVSLRKQTYVWTRSKHP  
SLMSINSDDVEKQSCDSTQALVTFTSSSITYDLPPSSVPSPAYPVTESCHLSSVAFVPCL

SEQ ID No:55

MEVDGTTPRRGGCKMPLPVQVFNLQGAVEPMQIDVDPQEDPQNAPDVNYVVENPSLDL  
EQYAASYSGLMRIERLQFIADHCPTLRVEALKMALSFVQRTFNVDMYEEIHRKLSEATR  
ELQNAPDAIPESGVEPPALDTAWVEATRKKALLKLEKLDTDLKNYKGNISIKESIRRGHDD  
LGDHYLDCGDLNALKCYSRARDYCTSAKHVINMCLNVIKVSVYLNWVSHVLSYVSKA  
ESTPEIAEQRGERDSQTQAILTKLKCAAGLAELAARKYKQAAKCLLLASFHDHCFPELLS  
PSNVAIYGGLCALATFDRQELQRNVISSSSFKLFLELEPQVRDIIFKFYESKYASCLKMLD  
EMKDNLLLDMYLAPHVRTLYTQIRNRALIQYFSPYVSADMHRMAAAFNNTTVALEDELT  
QLILEGLISARVDSHSHKILYARDVDQRSTTFEKSLLMGKEFQRRAKAMMLRAAVLRNQIH  
VKSPPREGSQGELTPANSQSRMSTNM

SEQ ID No:56

RRRRPSSSRRLRGRGAAQMACPALGLEALQPLQPEPPPEPAFSEAQKWIEQVTGRSF  
GDKDFRTGLENGILLCELLNAIKPGLVKKINRLPTPIAGLDNIILFLRGCKELGLKESQLFD  
PSDLQDTSNRVTVKSLDYSRKLKNVLVTIYWLGAANSCTSYSGTTLNLKEFEGLLAQM  
RKDTDDIESPKRSIRDSGYIDCWDSERSDSLSPPRHGRDDSFDSLDSFGSRSRQTPSP  
DVVLRGSSDGRGSDSESDLPHRKLPDVKKDDMSARRTSHGEPKSAVPFNQYLPNKS  
QTAYVPAPLRKKKAEREEYRKSWSTATSPLGGERPFRYGPRTPVSDDAESTSMFDMR  
CEEEAAVQPHSRARQEQLQLINNQLREEDDKWQDDLARWKSRRRSVSQDLIKKEER  
KKMEKLLAGEDGTSERRKSIKTYREIVQEKERRERELHEAYKNARSQEEAEGILQQYIE  
RFTISEAVLERLEMPKILERSHSTEPNLSSFLNDPNPMKYLRQQSLPPPKFTATVETTIAR  
ASVLDTSMSAGSGSPSKTVTPKAVPMLTPKPYSPKNSQDVLKTFKVDGKVSVNGETV  
HREEEKERECPTVAPAHSLTKSQMFEGVARVHGSPLELKQDNGSIEINIKKPNSVPQEL  
AATTEKTEPNSEQEDKNDGGKSRKGNIELASSEPHFTTTVTRCSPTVAFVEFPSSPQLK  
NDVSEEKQKKPENEMSGKVELVLSQKVVKPKSPEPEATLTFPFLDKMPEANQLHLPN  
LNSQVDSPSSEKSPVTTTPQFKFWAWDPPEEERRRQEKWQQEQERLLQERYQKEQDKL  
KEEWEKAQKEVEEEEERRYYEEERKIIEDTVVPFTVSSSSADQLSTSSSMTEGSGTMNKI  
DLGNCQDEKQDRRWKKSFGQDDSDLLKLTRESDRLEEKGSLTEGALAHSGNPVSKGV  
HEDHQLDTEAGAPHCGTNPQLAQDPSQNQQTSNPTHSSSEDKPKTLPLDKSINHQIES  
PSERRKKSPREHFQAGPFSPCSPTPPGQSPNRSISGKKLCSSCGLPLGKGAAMIETLN  
LYFHIQCFRCGICKGQLGDAVSGTDVRIRNGLLNCNDCYMRSRASAGQPTTL

SEQ ID No:57

MLIKVKTLTGKEIEIDIEPTDKVERIKERVEEKEGIPPQQQRLIYSGKQMNDEKTAADYKIL  
GGSVLHLVLALRGGGGLRQ

SEQ ID No:58

MVPEAWRSGLVSTGRVVGVLALLGALNKASTVIHYEIPEREKGFVGNVAVANLGLDLG  
SLSARRFRVVSGASRRFFEVRNRETGEMFVNDRDLREELCGTLPSCVTLELVVENPLEL  
FSVEVVIQDINDNPAFPTQEMKLEISEAVAPGTRFPLESAHDPDVGSNSLQTYELSRN  
EYFALRVQTTREDSTKYAELVLERALDREREPSLQLVLTALDGGTPALSASLPIHIKVLDA  
NDNAPVFNQSLYRARVLEDAPSGTRVVQVLATDLDEGPNGEIIYSFGSHNRAGVRQLF  
ALDLVTGMLTIKGRDLDFEDTKLHEIYIAKDKGANPEGAHCKVLVEVVDVNDNAPEITVT  
SVYSPVPEDAPLGTVIALLSVTDLDAENGLVTCEVPPGLPFSLTSSLKNYFTLKTSADL  
DRETVPEYNLSITARDAGTPSLSALTIVRVQVSDINDNPPQSSQSSYDVYIEENNLPGAPI  
LNLSVWDPDAPQNARLSFFLLEQGAETGLVGRYFTINRDNGIVSSVLPLDYEDRREFEL

TAHISDGGTPVLATNISVNIFVTDNRNDNAPQVLYPRPGGSSVEMLPRGTSAGHLVSRVV  
 GWDADAGHNAWLSYSLLGSPNQSLFAIGLHTGQISTARPVQDQDTPRQTLTVLIKDNGE  
 PSLSTTATLTVSVTEDSPEARAEFPGSAPREQKKNLTFYLLLSLILVSVGFVTVFGVIIF  
 KVKWKQSRDLRYRAPVSSLYRTPGPSLHADAVRGGLMSPHLYHQVYLTDSRRSDPLL  
 KKPGAASPLASRQNTLRSCDPVFYRQVLGAESAPPGQQAPPNTDWRFSQAQRPGTS  
 GSQNGDDTGTWPNNQFDTEMLQAMILASASEAADGSSTLGGGAGTMGLSARYGPQF  
 TLQHPDYRQNVYIPGSNATLTNAAGKRDGKAPAGGNGNKKKSGKKEKK

SEQ ID No:59

MAAAMDVDTPSGTNSGAGKKRFEVKKWNAVALWAWDIVVDNCAICRNHIMDLCECQA  
 NQASATSEECTVAWGVCNHAFHFHCISRWLKTRQVCPLDNREWEFQKYGH

SEQ ID No:60

MDADM DYERPNVETIKCVVVGDNVAVGKTRLICARACNTTLTQYQLLATHVPTVWAIQY  
 RVCQEV LERSRDVVDEVSVSLRLWDTFGDHHKDRRFAYGRSDVVVLCFSIANPNSLNH  
 VKSMWYPEIKHFCPRTPVILVGCQLDLRYADLEAVNRARRPLARPIKRGDILPPEKGREV  
 AKELGLPY YETSVFDQFGIKDVFDNAIRAALISRRHLQFWKSHLKKVQKPLLQAPFLPPK  
 APPPVIKIPECPSMGTNEAACLLDNPLCADVLFILQDQEHIFAHRIYLATSSSKFYDLFLM  
 ECEESPNGSEGACEKEKQSRDFQGRILSVDPEEEREEGPPRIPQADQWKSSNKSLEA  
 LGLEAEGAVPETQTLTGWSKGFIMHREM QVNPISKRMGPMTVVRMDASVQPGPFRT  
 LLQFLYTGQLDEKEKDLVGLAQIAEVLEMFDLRMMVENIMNKEAFMNQEITKAFHVRKA  
 NRIKECLSKGTFS DVTFLDDGAISAHKPL LICSC EWMAAMFGGSFVESANSEVYLPNIN  
 KISMQAVLDYLYTKQLSPNLDLDPLELIALANRFCLPHLVALAEQHAVQELTKAATSGVGI  
 DGEVLSYLELAQFHNAHQLAAWCLHHICTNYNSVCSKFRKEIKSKSADNQEYFERHRW  
 PPVWYLKEEDHYQRVKREREKEDIALNKHRSRRKWC FWNSSPAVA

SEQ ID No:61

ACSAGRDVFLTLEATPSHVVSRLMDSMDYERPNVETIKCVVVGDNVAVGKTRLICARA  
 CNATLTQYQLLATHVPTVWAIQYRVCQEV LERSRDVVDDVSVSLRLWDTFGDHHKDR  
 RFAYGRSDVVVLCFSIANPNSLHHVKT MWYPEIKHFCPRAPVILVGCQLDLRYADLEAV  
 NRARRPLARPIKPNEILPPEKGREVAKELGIPYYETSVVAQFGIKDVFDNAIRAALISRRH  
 LQFWKSHLRNVQRPLLQAPFLPPKPPPP IIVVPDPSSSEECPAHLLEDPLCADVILVLQ  
 ERVRIFAHKIYLSTSSSKFYDLFLMDLSEGELGGPSEPGGTHPEDHQGHSDQHHHHHH  
 HHHGRDFLLRAASF DVCESVDEAGGSGPAGLRASTSDGILRGNGTGYPGRGRVLSS



WSRAFVSIQEEMAEDPLTYKSRLMVVVKMDSSIQPGPFRAVLKYLYTGELDENERDLM  
 HIAHIAELLEVDLRRMMVANILNNEAFMNQEITKAFHVRRRTNRVKECLAKGTFSDVTFILD  
 DGTISAHKPLLISSCDWMAAMFGGPFVESSTREVVFPYTSKSCMRVLEYLYTGMFTSS  
 PDLDDMKLIILANRLCLPHLVALTEQYTVTGLMEATQMMVDIDGDVLVFLELAQFHCAYQ  
 LADWCLHHICTNYNNVCRKFPRDMKAMSPENQEYFEKHRWPPVWYLKEEDHYQRAR  
 KEREKEDYLHLKRQPKRRWLFWNSSPSSSAASSSSPSSSSSAVV

SEQ ID No:62

MAAAAAMAEQESARNGGRNRGGVQRVEGKLRAVEKGDYYEAHQMYRTLFFRYMSQ  
 SKHTEARELMYSGALLFFSHGQQNSAADLSMLVLESLEKAEVEVADELLENLAKVFSLM  
 DPNSPERVTFVSRALKWSSGGSGKLGHPRLHQLLALTLWKEQNYCESRYHFLHSADG  
 EGCANMLVEYSTSRGFRSEVDMFVAQAVLQFLCLKNKSSASVVFTTYTQKHPSIEDGP  
 PFVEPLLNFIFWLLAVDGGKLTVFTVLCEQYQPSLRRDPMYNEYLDRIGQLFFGVPPK  
 QTSSYGGLLGNLLTSLMGSSSEQEDGEESPSDGSPIELD

SEQ ID No:63

MIPESEDSFETMMEHKNPSSKQMESSEGGSSNTTEATSGSGVRGEAGPASGPAQEKK  
 PPSGPLQEMEELPTDLLQDMEEPSSGPRKEIEDPPNDLLQDLEESCNGSHQARGDPLS  
 GASDRMKEASVNP SGAREEQEAHTDLKESGREETPQEQNQTEHSTAELMAMVRSIISL  
 YFRMQDLKEQQRVAEEILIKGINAGQLPAPKHFSGDRREFHEFIVLCQLTLQSYPRMFY  
 NDRLRVGYVINHL SGLALEWAKALLQENSPLIGDFPAFLEAMSEVFEYRQALRVAEEAM  
 FTIRQGGRSATEYIDEFQSLVPILGWPDEV LQAHL CQGLNEEIRHYLFRVPQPD SLDSLI  
 VLILQIEEKLAERRAMLRLPPEARPRNL TWIDSPAPERWMVSSWLPSEVHPDINRAHLFL  
 LLMVRVNPYHSVAVQALVD SGADGNFMDEKFAQEHYVELYEKPYQPQVQSVDGSLIGN  
 EPVWLYTEPLVCIHQNHQESIEFDIVPSPNFSVVLGIRWLRVHAPEVDWIKGRCTFHSPY  
 CLKNCFRPPPPCIALERHGMSLLPGLPHPYSDLADVFNPKEADDETS DQPS SDGSDDL  
 SESEPSSELQQAGDS DHSETFY ECPSTAPWEPVGARMQERARLQEEYWDLQDMLTNR  
 QDYIQMIPELFDQLHGAEWFTKLELRGTIVEESVNGHRTEDVWKA AFGLELEEMKSYQP  
 FALSPDPIIPQNVIHFILK DMLGFFVLSYGQEVLIYSMSQEEHLHHVRQVLVRFRHHNVY  
 CSLDKSQFHRQTVEFLGFVVT PKGVKLNKNVMTITGYPTPGSKLSLRNFIEFVFPYRHF  
 VERFSIIAEPLVRQLLSSYQFYWGVEEQEAFECLKRAFRKAPLLHHPKPQNPFYLETGV  
 TGTALHASLIQIDDQTGKRACCAFYSRNISPIEVEYSQAEMKILPIRAAFMVWCRYLENTE  
 EPIMILLNTEDLASLNNDR LTVLLPGHWWFFF SHFNFDVMELPEQDGGRALPPVRNLRW  
 RRAFQRNTAARQTLLLASRGFPRDPSTESGEEENE EQDELNEQILRQELLAMIPIDQILN

SFLAHFSMAQIRAVILHFFRGLLYWKNTLALAAILVLLRVRQCCLSLRPAPAMRVARPQPQ  
 RSLRLILDSSLIAGSSITTAITQLLTQMPALVGANTIPAQELAELFLGPGRWQRNALHSQA  
 HRGLQFTPGFWLTLCEFFGVRVTPQEGHLPALRQNRYLELHVVGDEDEDVVLREALQDDL  
 QRYRQCGLHDGLQDTSQDKQDNDVQEAPPSHTAATHPPRPRHLMDPQVLEFLGSRL  
 HIHSADGQLHLLSREQAARALSQFLTLIYRRALPIPAWESQPREQARLEELPDEDEDANL  
 D

SEQ ID No:64

MSDMEDDFMCDDEEDYDLEYSEDSNSEPNVDLENQYYNSKALKEDDPKAALSSSFQKV  
 LELEGEKGEWGFKALKQMIKINFKLTFPEMMNRYKQLLTYIRSAVTRNYSEKSINSILD  
 YISTSKQMDLLQEFYETTLEALKDAKNDRLWFKTNTKLGKLYLEREEYGKLQKILRQLHQ  
 SCQTDDGEDDLKKGTLLEIYALEIQMYTAQKNNKKLKALYEQSLHIKSAIPHPLIMGVIR  
 ECGGKMHLREGEFEKAHTDFFFAFKNYDESGSPRRTTCLKYLVLANMLMKSGINPFDS  
 QEAKPYKNDPEILAMTNLVSAYQNNDITEFEKILKTNHSNIMDDPFIREHIEELLRNIRTQV  
 LIKLIKPYTRIHIPFISKELNIDVADVESLLVQCILDNTIHGRIDQVNLLELDHQKRGGARY  
 TALDKWTNQLNSLNQAVVSKLA

SEQ ID No:65

MATPDQKSPNVLLQNLCCRILGRSEADVAQQFQYAVRVIGSNFAPTVERDEFLVAEKIK  
 KELIRQRREADAALFSELHRKLHSQGVLKNKWSILYLLLSLSEDPRRQPSKVSSYATLFA  
 QALPRDAHSTPYYYARPQTLPLSYQDRSAQSAQSSGSGVSSGSISSIGLCALSGPAPAP  
 QSLLPGQSNQAPGVGDCLRQQLGSRLAWTLTANQPSSQATTSSKGVPSAVSRNMTRSR  
 REGDTGGTMEITEAALVRDILYVFQIDGKNIKMNNTENCYKVEGKANLSRSLRDTAVR  
 LSELGWLHNKIRRYTDQRS�DRSFLVGQSFCALHQELREYYRLLSVLHSQLQLEDD  
 QGVNLGLESSLTLRRLLVWTDYDPKIRLKTALVDHCQGRKGGELASAVHAYTKTGDPY  
 MRSLVQHILSLVSHPVLSFLYRWIYDGELEDYHEFFVASDPTVKTDRLLWHDKYTLRKS  
 MIPSFMTMDQSRKVLLIGKSINFLHQVCHDQTPTTKMIAVTKSAESPQDAADLFTDLENA  
 FQGKIDAAYFETSKYLLDVLNKKYSLLDHMQAMRRYLLLGQGFIRHLMDLLKPELVRP  
 ATTLYQHNLTGILETAVRATNAQFDSPEILRRLDVRLLLEVSPGDTGWDVFSLDYHVDGPI  
 ATVFTRECMASHYLRVFNFLWRAKRMETILTDIRKGHMCNAKLLRNMPEFSGVLHQCHIL  
 ASEMVFHFIHQMQYYITFEVLECSWDELWNKVQQAQDLHDHIIAAHEVFLDTIISRCLLDSD  
 SRALLNQLRAVFDQIIELQNAQDAIYRAALEELQRRRLQFEEKKKQREIEGQWGVTAEE  
 EEENKRIGEFKESIPKMCSQLRILTHFYQGIVQQFLVLLTTSSDESRLRFLSFRLDNFNEHYK  
 AREPRLRVSLGTRGRRSSHT

SEQ ID No:66

MAVAPRLFGGLCFRFRDQNPEVAVEGRLPISHSCVGCRRERTAMATVAANPAAAAAAV  
AAAAAVTEDREPQHEELPGLDSQWRQIENGESGRERPLRAGESWFLVEKHWYKQWE  
AYVQGGDQDSSTFPGCINNATLFQDEINWRLKEGLVEGEDYVLLPAAAWHYLVSWYGL  
EHGQPPIERKVIELPNIQKVEVYPVELLLVRHNDLGKSHTVQFSHTDSIGLVLRTARERFL  
VEPQEDTRLWAKNSEGSLDRLYDTHITVLDALETGQLIIMETRKKDGTWPSAQLHVMN  
NNMSEDEDFKGGQPGICGLTNLGNTCFMNSALQCLSNVPQLTEYFLNNCYLEELNFRN  
PLGMKGIEIAEAYADLVKQAWSGHHRSIVPHVFKNKVGHFASQFLGYQQHDSQELLSFL  
LDGLHEDLNRVKKKEYVELCDAAGRPDQEVAAQWQNHKRRNDSVIVDTFHGLFKSTL  
VCPDCGNVSVTFDPFCYLSVPLPISHKRVLEVFFIPMDPRRKPEQHRLVVPKKGKISDLC  
VALSKHTGISPERMMVADVFSHRFYKLYQLEEPSSILDRDDIFVYEVSGRIEAIEGSRED  
IVPVYLRETRTPARDYNNSYYGLMLFGHPLLVSVPDRDFTWEGLYNVLMYRLSRYVTK  
PNSDDEDDGDEKEDDEEDKDDVPGPSTGGSLRDPEPEQAGPSSGVTNRCPFLLDNCL  
GTSQWPPRRRRRKQLFTLQTVNSNGTSDRTTSPEEVHAQPYIAIDWEPKRYDEVE  
AEGYVKHDCVGYVMKKAPVRLQECIELFTTVETLEKENPWYCPSCQHQQLATKKLDLW  
MLPEILIIHLKRFSYTKFSREKLDTLVEFPIRDLDSEFVIQPNESNPELYKYDLIAVSNH  
YGGMRDGHYTTFACNKDSGQWHYFDDNSVSPVNENQIESKAAYVLFYQRQDVARRLL  
SPAGSSGAPASPACSSPPSSEFMDVN

SEQ ID No:67

MPVRKQDTQRALHLL EEYRSKLSQTEDRQLRSSIERVINIFQSNLFQALIDIQEFYEVTL  
DNPKCIDRSKPSEPIQPVNTWEISSLPSTVTSETLPSSLSPSVEKYRYQDEDTPPQEH  
SPQITNEVIGPELVHVSEKNLSEIENVHGFVSHSHISPIKPTAVLPSPPTVPVIPVLPVPA  
ENTVILPTIPQANPPPVLVNTDSLETPTYVNGTDADYEYEEITLERGNSGLGFSIAGGTD  
NPHIGDDSSIFITKIITGGAAAQDGRRLRVNDCILQVNEVDVRDVTHSKAVEALKEAGSIVR  
LYVKRRKPVSEKIMEIKLIKGPGLGFSIAGGVGNQHIPGDNSIYVTKIIEGGAHKDGKL  
QIGDKLLAVNNVCLEEVTHEEAVTALKNTSDFVYLKVAKPTSMYMN DGYAPPDITNSSS  
QPVDNHVSPSSFLGQTPASPARYSPVSKAVLGDDEITREPRKVVLHRGSTGLGFNIVG  
GEDGEGIFISFILAGGPADLSGELRKGDRIISVNSVDLRAASHEQAAAALKNAGQAVTIVA  
QYRPEEYSRFEAKIHD LREQMMNSSISSGSGSLRTSQKRSLYVRALFDYDKTKDGLP  
SQGLNFKFGDILHVINASDDEWWQARQVTPDGESDEVGVIPSKRRVEKKERARLKTVK  
FNSKTRDKGQSFNDRKKNLFSRKFPFYKNKDQSEQETSDADQHVTSNASDSESSYR  
GQEEYVLSYEPVNQQEVNYTRPVILGPMKDRINDDLISEFPDKFGSCVPHTTRPKRDY

EVDGRDYHFVTSREQMEKDIQEHKFIEAGQYNNHLYGTSVQSVREVAGKGKHCILDVS  
GNAIKRLQIAQLYPISIFIKPKSMENIMEMNKRLTEEQARKTFERAMKLEQEFTTEHFTAIV  
QGDTLEDIYNQVKQIIIEEQSGSYIWVPAKEKL

SEQ ID No:68

DLTQAKPIYGGWLLLAPDGTDFDNPVHRSRKWQRRFFILYEHGLLRYALDEMP TTLPQ  
GTINMNQCTDVVDGEGRTGQKFSLCILTPEKEHFIRAETKEIVSGWLEMLMVYPRTNKQ  
NQKKKRKVEPPTPQEPGPAKVAVTSSSSSSSSSSSIPSAEKVPTTKSTLWQEEMRTKDQ  
PDGSSLSPAQSPSQSQPPAASSLREPGLESKEEESAMSSDRMDCGRKVRVESGYFSL  
EKTKQDLKAEQQQLPPPLSPPSPSTPNHRRSQVIEKFEALDIEKAEHMETNAVGPSQSS  
DTRQGRSEKRAFPRKRDFTEAPPAPLPDASASPLSPHRRAKSLDRRSTEPSVTPDLL  
NFKKGWLTQYEDGQWKHWFLADQSLRYRDSVAEEAADLDGEIDLACDYDTEY  
PVQRNYGFQIHTKEGEFTLSAMTSGIRRNWIQTIMKHVHPTTAPDVTSSLPEEKNKSSC  
SFETCPRPTEKQEAELGEPDPEQKRSRARRERRREGRSKTFDWAEFRLIQQALAQERV  
GGVGPADTHEPLRPEAEPGELERERARRREERRKRFGMLDATDGPGTEDAALRMEVD  
RSPGLPMSDLKTHNVHVEIEQRWHQVETTP LREEKQVPIAPVHLSSSEDGGDRLSTHEL  
TSLLEKELEQSQKEASDLLEQNRLQLDQLRVALGREQSAREGYVLQATCERGF AAMEE  
THQKKIEDLQRQHORELEKLREEKDRLLAEETAATISAIEAMKNAHREEMERELEKSQR  
SQISSVNSDVEALRRQYLEELQSVQRELEV LSEQYSQKCLENAHLAQALEAERQALRQ  
CQRENQELNAHNQELNNRLAAEITRLRTL TGDGGGEATGSPLAQQKDAYELEVLLRV  
KESEIQYLKQEISSLKDELQ TALRDKKYASDKYKDIYTELSIAKAKADCDISR LKEQLKAAT  
EALGEKSPDSATVSGYDIMKSKSNPDLK KDRSCVTRQLRNIRSKSVIEQVSWDT

SEQ ID No:69

MAGITTIEAVKRKIQVLQQQADDAEERAERLQREVEGEKMEQLQEIQ LKEAKHIAEEADRK  
YEEVARKLVIIEGDLERTEERAELAESRCREMDEQIRLMDQNLKCLSA AE EKYSQKEDK  
YEEEIKILTDKLKEAETRAEFAERSVAKLEKTIDDLEDKLKCTKEEHLCTQRMLDQTLLDL  
NEM

SEQ ID No:70

MACPALGLEALQPLQPEPPPEPAFSEAQKWIEQVTGRSFGDKDFRTGLENGILLCELLN  
AIKPGLVKKINRLPTPIAGLDNIILFLRGCKELGLKESQLFDP SLDLQDTSNRVTVKSLDYSR  
KLKNVLVTIYWLGKAANSCTSYSGTTNLKEFEGLLAQMRKDTDDIESPKRSIRD SGYID  
CWDSESRSDSLSPPRHGRDDSFDSLDSFGSRSRQTPSPDVVLRGSSDGRGSDSESDLP

HRKLPDVKKDDMSARRTSHGEPKSAVPFNQYLPNKSNTAYVPAPLRKKKAEREEYR  
KSWSTATSPLGGERPFRYPRTVPVSDDAESTSMFDMRCEEEAAVQPHSRARQEQLQL  
INNQLREEDDKWQDDLARWKSRRRSVSQDLIKKEEERKKMEKLLAGEDGTSERRRSIK  
TYREIVQEKERRERELHEAYKNARSQEEAEGILQQYIERFTISEAVLERLEMPKILERSHS  
TEPNLSSFLNDPNPMKYLRQQSLPPPFTATVETTIARASVLDTSMSAGSGSPSKTVTP  
KAVPMLTPKPYSQPKN SQDVLKTFKVDGKVS VNGETVHREEEKERECPTVAPAHSLTK  
SQMFEGVARVHGSPLELKQDNGSIEINIKKPNSVPQELAAATTEKTEPN SQEDKNDGGKS  
RKGNIELASSEPHFTTTVTRCSPTVAFVEFPSSPQLKNDVSEEKDQKKPENEMSGKV  
ELVLSQKVVKPKSPEPEATLTFPFLDKMPEANQLHLPNLNSQVDSPTSSEKSPVMTPFKF  
WAWDPEEERRRQEKWQQEQERLLQERYQKEQDKLKEEWEKAQKEVEEEEERRYYEE  
ERKIIEDTVVPFTVSSSSADQLSTSSSMTEGSGTMNKIDLGNCQDEKQDRRWKKSFGQ  
DDSDLLLKTRESDRLEEKGSLTEGALAHSGNPVSKGVHEDHQLDTEAGAPHCGTNPQL  
AQDPSQNNQTSNPTHSSSEDVKPKTLPLDKSINHQIESPSERRKKSPREHFQAGPFSPC  
SPTPPGQSPNRSISGKKLCSSCGLPLGKGAAMIIETLNLYFHIQCFRCGICKGQLGDAVS  
GTDVIRIRNGLLNCNDCYMRSRSAGQPTTL

SEQ ID No:71

PLCPALCPTSPPLPLPPSVSPPGCLTLWSLSFLFSVPSAPYPHLKTTMATIPDWKLQL  
LARRRQEEASVRGREKAERERLSQMPAWKRGLLERRRAKLGLSPGEPSPVLGTVEAG  
PPDPDESAVLLEAIGPVHQNRFIRQERQQQQQQQQRSEELLAERKPGPLEARERRPSP  
GEMRDQSPKGRESREERLSPRETRERRLGIGGAQELSLRPLEARDWRQSPGEVGD RS  
SRLSEAWKWRLSPGETPERSLRLAESREQSPRRKEVESRLSPGESAYQKLGLTEAHK  
WRPDSRESQEQSLVQLEATEWRLRSGEERQDYSEECGRKEEWPVPGVAPKETAELS  
ETLTREAQGNSSAGVEAAEQRPVEDGERGMKPTGKWTNLNSGKAREWTPRDIEAQ  
TQKPEPPESA EKLLESPGVEAGEGEAEKEEAGAQRPLRALQNCCSVPSPLPPEDAGT  
GGLRQQEEEEAVELQPPPPAPLSPPPPAPTAPQPPGDPLMSRLFYGVKAGPGVGAPRR  
SGHTFTVNPRRSVPPATPATPTSPATVDAAVPGAGKKRYPTAE EILVLGGYLRLSRCL  
AKGSPERHHKQLKISFSETALETYQYPSESSVLEELGPEPEVPSAPNPPAAQPDDEED  
EEELLLLQPELQGGRLRTKALIVDESCRR

SEQ ID No:72

MTSAAPAKKPYRKAPPEHRELRL EIPGSRLEQEEPLTDAERMKLLQEENEELRRRLASA  
TRRTEALERELEIGQDCLELELGQSREELDKFKDKFRRLQNSYASQRTNQELEDKLHT  
LIKKAEMDRKTL DWEIVELTNKLLDAKNTINKLEELNERYRLDCNPAVQLLCKNKSHFRN

HKFADLPCELQDMVRKHLHSGQEAAASPGPAPSLAPGAVVPTSVIARVLEKPESLLLNSA  
 QSGSAGRPLAEDVVFVHVDMSSEGVPGDPASPPAPGSPTPQPNGECHSLGTARGSPEEE  
 LPLPAFEKLNYPYPTPSPPHPLYPGRRVIEFSEDKVRIPRNSPLPNCTYATRQAISLSLVEE  
 GSERARPSVPSTPASAQASPHHQPSPAPLTLSAPASSASSEEDLLVSWQRAFVDRT  
 PPAAVAQRTAFGRDALPELQRHFAHSPADRDEVVQAPSARPEESELLLPTEPDSGFPR  
 EEEELNLPISPEEERQSLPINRGTEEGPGTSHTEGRAWPLPSSSRPQRSPKRMGVHH  
 LHRKDSLTAQAEQGNLLN

SEQ ID No:73

MASTISAYKEKMKELSVLSLICSCFYTQPHPNTVYQYGDMEVKQLDKRASGQSFEVILK  
 SPSDLSPESPMLSSPPKKKDOTSLEELQKRLEAAEERRKTQEAQVLKQLAERREHEREV  
 LHKALEENNNFSRQAEKLNKYMELSKEREHLAALRERLREKELHAAEVRNKEQRE  
 MSG

SEQ ID No:74

MAHRKLESVSGSMLDHRVRPGVPVPHSQEPESEDMELPLEGYVPEGLELAALRPESPA  
 PEEQECHNHSPDGDSSSDYVNNTSEEEDYDEGLPEEEEGITYYIRYCPEDDSYLEGMD  
 CNGEEYLAHSAHPVDTDECQEAVEEWTDGAGPHPHGHEAEGSQDYPDGQLPIPEDEP  
 SVLEAHDQEEDGHYCASKEGYQDYYPEEANGNTGASPYRLRRGDGDLEDQEEDIDQI  
 VAEIKMSLSMTSITSASEASPEHGPEPGPEDSVEACPPIKASCSPSRHEARPKSLNLLPE  
 AKHPGDPQRGFKPKTRTPEERLKWPHQVCNGLEQPRKQQRSDLNPNIPETK  
 KVASFSPFVAVPGPCEPEDLIDGIIFAANYLGSTQLLSERNPSKNIRMMQAQEA VSRVKR  
 MQKAAKIKKKANSEGDAQTLTEVDLFISTQRIKVLNADTQETMMDHALRTISYIADIGNIV  
 VLMARRRMPRSASQDCIETTPGAQEGKKQYKMICHVFESDAQLIAQSIGQAFSVAYQ  
 EFLRANGINPEDLSQKEYSDIINTQEMYNDLIHFSNSENCKELQLEKHKGELGVVVE  
 SGWGSILPTVILANMMNGGPAARSGKLSIGDQIMSINGTSLVGLPLATCQGIKGLKNQT  
 QVKLNIVSCPPVTTVLIKRPDLKYQLGFSVQNGIICSLMRGGIAERGGVRVGHRIIEINGQ  
 SVVATAHEKIVQALSNSVGEIHMKTMPAAMFRLLTGQETPLYI

SEQ ID No:75

MQRVPEGFGRRLGSDMGNAERAPGSRSFGPVPTLLLLAAALLAVSDALGRPSEEDE  
 ELVVPELERAPGHGTTRLRLHAFDQQLDLELRPDSSFLAPGFTLQNVGRKSGSETPLPE  
 TDLAHCIFYSGTVNGDPSSAAALSLCEGVRGAFYLLGEAYFIQPLPAASERLATAAPGEK  
 PPAPLQFHLLRRNRQGDVGGTCGVVDDEPRPTGKAETEDEDEGTEGEDEGPQWSPQ

DPALQGVGQPTGTGSIRKKRFVSSHRYVETMLVADQSMAEFHGSGGLKHYLLTLFSVAA  
RLYKHPSIRNSVSLVVVKILVIHDEQKGPEVTSNAALTLRNFCNWQKQHNPPSDRDAEH  
YDTAILFTRQDLCGSQTCDTLGMADVGTVCPSRSCSVIEDDGLQAAFTTAHELGHVFN  
MPHDDAKQCASLNGVNQDSHMMASMLSNLDHSQPWSPCSAYMITSFLDNHGHECLM  
DKPQNPIQLPGDLPGTSYDANRQCQFTFGEDSKHCPDAASTCSTLWCTGTSGGVLC  
QTKHFPWADGTSCGEGKWCINGKCVNKTDRKHFDTPFHGSWGMWGPWGDCSRTCG  
GGVQYTMRECDNPVPKNGGKYCEGKRVRYRSCNLEDCPDNNGKTFREEQCEAHNEF  
SKASFGSGPAVEWIPKYAGVSPKDRCKLICQAKGIGYFFVLQPKVVDGTPCSPDSTSVC  
VQGQCVKAGCDRIIDSKKKFDKCGVCGGNGSTCKKISGSVTSAPKGYHDIITPTGATNI  
EVKQRNQRGSRNNGSFLAIKAADGTIYILNGDYTLSTLEQDIMYKGVVLRYSGSSAALERI  
RSFSPLKEPLTIQVLTVGNALRPKIKYTYFVKKKKESFNAIPTFSAWVIEEWGECSKSC  
ELGWQRRRLVECRDINGQPASECAKEVKPASTRPCADHPCPQWQLGEWSSCSKTCGKGY  
KKRSLKCLSHDGGVLSHESCDPLKKPKHFIDFCTMAECS

SEQ ID No:76

MRLTHICCCCLLYQLGFLSNGIVSELQFAPDREEWEVFPALWRREPVDPAAGSGGSA  
DPGWVRGVGGGGSARAQAAGSSREVRVAPVPLEEPVEGRSESRLRPPPPSEGEED  
EELESQELPRGSSGAAALSPGAPASWQPPPPPQPPPSPPPAQHAEPDGDEVLLRIPAF  
SRDLYLLLRRDGRFLAPRFAVEQRPNP GPGPTGAASAPQPPAPPDAGCFYTGAVLRHP  
GSLASFSTCGGGLMGFIQLNEDFIFIEPLNDTMAITGHPHRVYRQKRSMEEKVTEKSAL  
HSHYCGIISDKGRPRSRKIAESGRGKRYSYKLPQEYNIETVVVADPAMVSYHGADAARR  
FILTILNMVFNLFQHKSLGVQVNLRVIKLILLHETPPELYIGHHGEKMLESFCKWQHEEFG  
KKNDIHLEMSTNWGEDMTSVDAAILITRKDFCVHKDEPCDTVGIAYLSGMCSEKRCIIA  
EDNGLNLAFTIAHEMGMHNGINHDNDHPSCADGLHMSGEWIKGQNLGDVSWSRCSK  
EDLERFLRSKASNCLLQTNPQSVNSVMVPSKLPGMTYTADEQCQILFGPLASFCQEMQ  
HVICTGLWCKVEGEKECRTKLDPPMDGTDCDLGWCKAGECTSR TSAPEHLAGEWSL  
WSPCSRTCSAGISSRERKCPGLDSEARDCNGPRKQYRICENPPCPAGLPGFRDWQCC  
AYSVRTSSPKHILQWQAVLDEEKPCALFCSPVGKEQPILLSEKVM DGTSCGYQGLDICA  
NGRCQKVGCDGLLGLSLAREDHCGVCNGNGKSKKIIKGDFNHTRGAGYVEVLVIPAGAR  
RIKVVEEKPAHSYLALRDAGKQSINSDWKIEHSGAFNLAGTTVHYVRRGLWEKISAKGP  
TTAPLHLLVLLFQDQNYGLHYEY TIPS DPLPENQSSKAPEPLFMWTHTSWEDCDATCG  
GGERKTTV SCKIMSKNISIVDNEKCKYLTKPEPQIRK CNEQPCQTRWMMTEWTPCSR  
TCGKGMQSRQVACTQQLSNGTLIRARERDCIGPKPASAQRCEGQDCMTVWEAGVWS  
EFSVKCGKGIRHRTVRCTNPRKKCVLSTRPREAEDCEDYSKCYVWRMGDWSKCSITC

GKGMQSRVIQCMHKITGRHGNECFSSSEKPAAYRPCHLQPCNEKINVNTITSPRLAALTF  
KCLGDQWPVYCRVIREKNLCQDMRWYQRCCECTCRDFYAQKLQQKS

SEQ ID No:77

MPGGPSPRSPAPLLRPLLLLLCALAPGAPGAPGRATEGRAALDIVHPVRVDAGGSFLS  
YELWPRALRKRDVSVRRDAPAFYELQYRGRELRFNLTANQHLLAPGFVSETRRRGGL  
GRAHIRAHTPACHLLGEVQDPELEGGLAAISACDGLKGVFQLSNEDYFIEPLDSAPARP  
GHAQPHVVYKRQAPERLAQRGDSSAPSTCGVQVYPELESRRERWEQRQQWRRPRL  
RRLHQRSVSKEKWVETLVVADAKMVEYHGQPQVESYVLTIMNMVAGLFHDP SIGNPIHI  
TIVRLVLLEDEEEDLKITHHADNTLKSFCKWQKSINMKGDAHPLHHDTAILLTRKDLCAA  
MNRPCETLGLSHVAGMCQPHRSCSINEDTGLPLAFTVAHELGHSGFIQHDGSGNDCEP  
VGKRPFIMSPQLLYDAAPLTWSRCSRQYITRFLDRGWGLCLDDPPAKDIIDFPSVPPGV  
LYDVSHQCRLQYGAYSAFCEMDNVCHTLWCSVGTTCHSKLDAAVDGTRCGENKWC  
LSGECVPVGFPEAVDGGWSGWSAWSICSRSCGMGVQSAERQCTQPTPKYKGRYC  
VGERKRFRLCNLQACPAGRPSFRHVQC SHFDAMLYKGQLHTWVPVNDVNPCELHC  
RPANEYFAKKLRDAVVDGTPCYQVRASRDLCINGICKNVGCDFEIDSGAMEDRCGVCH  
GNGSTCHTVSGTFEEAEGLGYVDVGLIPAGAREIRIQEVAEAAANFLALRSEDPEKYFLN  
GGWTIQWNGDYQVAGTTFTYARRGNWENLTSPGPTKEPVWIQVPASRGPGGGSRGG  
VPRPSTLHGRSRPGGVSPGSVTEPGSEPGPPAAASTSVSPSLKWPNLVAAVHRGGW  
GQAPLGLGGWRRHLVLMGPRLPTQLLFQESNPGVHYEYTIHREAGGHDEVPPPVSFWS  
HYGPWTKCTVTTCGRGEKWGRHSPTCRGLVSGQGHWLQLPAHCWATTGLEVCFSEP  
QFSICEMRLAIALCPRPAGRVHG

SEQ ID No:78

MAARGSGPRALRLLLLVQLVAGALRSSRARARRGLSEPSSI AKHEDSLLKDLFQDYE  
RWVRPVEHLNDKIKIKIFGLAISQLVDVDEKNQLMTTNVWLKQEWIDVKLRWNPDDYGGI  
KVIRVPSDSSWTPDIVLFDNADGRFEGTSTKTVIRYNGTVTWTPPANYKSSCTIDVTFFP  
FDLQNC SMKFGSWTYDGSQVDIILEDQDVKRDFFDNGEWEIVSATGSKGNRTDSCC  
WYPYVTYSFVIKRLPLFYTLFLIIPCIGLSFLT VLVFYLP SNEGEKICLCTSVLVSLTVFLLVI  
EEIIPSSSKVIPLIGEYLVFTMIFVTLSIMVTVFAINIHHRSSSTHNAMAPLVRKIFLHTLPKL  
LSMRSHVD RYFTQKEETESGSGPKSSRNTLEAALDSIRYITTHIMKENDVREVVEDWKFI  
AQVLDRMFLWTF L FVSIVGSLGLFVPVIYKWANILIPVHIGNANK

SEQ ID No:79



MEPGRRGAAALLALLCVACALRAGRAQYERYSFRRSFPDELMPLESAYRHALDKYSGE  
HWAESVGYLEISLRLHRLLRDSEAFCHRNCSAAPQPEPAAGLASYPELRLFGGLLRRAH  
CLKRCKQGLPAFRQSQPSREVLADFQRREPYKFLQFAYFKANNLPKAAAAHTFLLKHP  
DDEMMKRNMAYYKSLPGAEDYIKDLETKSYESLFIRAVRAYNGENWRTSITDMELALPD  
FFKAFYECLAACEGSREIKDFKDFYLSIADHYVEVLECKIQCEENLTPVIGGYPVEKFVAT  
MYHYLQFAYYKLNDLKNAAPCAVSYLLFDQNDKVMQQNLVYYQYHRDTWGLSDEHFQ  
PRPEAVQFFNVTTLQKELYDFAKENIMDDDEGEVVEYVDDLLELEETS

SEQ ID No:80

MGKVRGLRARVHQAAVRPKGEAAPGPAPPAPEATPPPASAAGKDWFINTNIFARTKI  
DPSALVQKLELDVRSVTSVRRGEAGSSARSVPSIRRGAEAKTVLPKKEKMKLRREQWL  
QKIEAIKLAEQKHREERRRRATVVVGDLHPLRDALPELLGLEAGSRRQARSRESNKPRP  
SELSRMSAAQRQQLLEEERTRFQELLASPAYRASPLVAIGQTLARQMQLDGGQL

SEQ ID No:81

MKLPARVFFTLGSRLPCGLAPRRFFSYGTKILYQNTEALQSKFFSPLQKAMLPPNSFQG  
KVAFITGGGTGLGKGMTTLLSSLGAQCVIASRKMDVLKATAEQISSQTGNKVHAIQCDV  
RDPDMVQNTVSELIKVAGHPNIVINNAAGNFISPTERLSPNAWKTITDIVLNGTAFVTLEI  
GKQLIKAQKGAAFLSITTIYAETGSGFVVPSSASAKAGVEAMSKSLAAEWGKYGMRFNVI  
QPGPIKTKGAFSRLDPTGTFEKEMIGRIPCGR LGTVEELANLAAFLCSDYASWINGAVIK  
FDGGEEVLISGEFNDLRKVTKEQWDTIEELIRKTKGS

SEQ ID No:82

MVAPGSVTSRLGSVFPFLLVLVDLQYEGAECGVNADVEKHLELGKKLLAAGQLADALS  
QFHAADVGDPDNYIAYYRRATVFLAMGKSKAALPDLTKVIQLKMDFTAARLQRGHLLK  
QGKLDEAEDDFKKVLKSNPSENEEKEAQSQLIKSDQMRLRSQALNAFGSGDYTAIAF  
LDKILEVCVWDAELRELRAECFIKEGEPRKAISDLKAASKLKNDNTEAFYKISTLYYQLGD  
HELSSLSEVRECLKLDQDHKRCFAHYKQVKKLNKLIESAEELIRDGRYTDATSKYESVMK  
TEPSIAEYTVRSKERICHCFSKDEKPVEAIRVCSEVLQMEPDNVNALKDRAEAYLIEEMY  
DEAIQDYETAQEHNENDQQIREGLEKAQRLLKQSQKRDYYKILGVKRNAKKQEIIKAYRK  
LALQWHPDNFQNEEEKKKAEEKFIDIAAAKEVLSDPEMRKKFDDGEDPLDAESQQGGG  
GNPFHRSWNSWQGFNPFSSGGPFRFKFHFN

SEQ ID No:83

MRPRKAFLLLLLLGLVQLLAVAGAEGPDEDSSNRENAIEDEEEEEEEEDDDEEEDDLEVK  
EENGVLVLNDANFDNFVADKDTVLLIFYAPWCGHCKQFAPEYEKIANILKDKDPPIPAK  
IDATSASVLASRFDVSGYPTIKILKKGQAVDYEGSRTQEEIVAKVREVSQPDWTPPEVT  
LVLTKENFDEVVNDADIILVEFYAPWCGHCKKLAPEYEKAAKELSKRSPPIPLAKVDATA  
ETDLAKRFDVSGYPTLKIFRKGRPYDYNGPREKYGIVDYMIEQSGPPSKEILTLKQVQEF  
LKDGDDVIIIIGVFKGESDPAYQQYQDAANNLREDYKFHHTFSTEIAKFLKVSQGQLVVM  
QPEKFQSKYEPRSHMMDVQGSTQDSAIDFVLKYALPLVGHRKVSNDKRYTRRPLVV  
VYYSVDFSFDYRAATQFWRSKVLEVAKDFPEYTFIADEEDYAGEVKDLGLSESGEDV  
NAAILDESGKKFAMEPEEFDSDLREFVTAFFKKGKLKPVIKSQPVPKNNKGPVKVVVGK  
TFDSIVMDPKKDVLIIFYAPWCGHCKQLEPVYNLSLAKKYKGQKGLVIKMDATANDVPS  
DRYKVEGFPTIYFAPSGDKKNPVKFEGGDRDLEHLSKFIEEHATKLSRTKEEL

SEQ ID No:84

MPEQSNDYRVVVFAGAGVGKSSLVLRVKGTFRDYIPTIEDTYRQVISCDKSVCTLQIT  
DTTGSHQFPAMQRLSISKGHAFILVFSVTSKQSLEELGPIYKLIVQIKGSVEDIPVMLVGN  
KCDETQREVDTREAQAVAQEWKCAFMETSAKMNYNVKELFQELLTLETRRNMSLNIDG  
KRSGKQKRTDRVKGKCTLM

SEQ ID No:85

MHLQMREDMAKYRRMSGVRPQSFRDLETPPHWAAYDTGLELLGRQEAGLALPRLEEA  
LQGSQAQMESCRADCEGPEEQQGAEEEEEDGAASQGGLYEAIAGHWIQVLQCRQRCV  
GEAATRPGRSFPVPDFLPNQLRRLHEAHAQVGNLSQAIENVLSVLLFYPEDEAAKRALN  
QYQAQLGEPRPGLGPREDIQRFILRSLGEKRQLYYAMEHLGTSFKDPDPWTPAALIPEA  
LREKLREDQEKRPWDHEPVKPKPLTYWKDVLLLEGVTLTQDSRQLNGSERAVLDGLLT  
PAECGVLLQLAKDAAGAGARSGYRGRSPHTPHERFEGTLVLKAAQLARAGTVGSQG  
AKLLEVSERVRTLTAQYFSPERPLHLSFTHLVCRSAIEGEQEQRMDLSHPVHADNCVL  
DPDTGECWREPPAYTYRDYSGLLYLNDDFQGGDLFFTEPNALTVTARVRPRCGRVAF  
SSGVENPHGVWAVTRGRRCALALWHTWAPEHREQEWIEAKELLQESQEEEEEEEEEE  
MPSKDPSPEPPSRRHQRVQDKTGRAPRVREEL

SEQ ID No:86

SLRLCPWGTLAGPTTMRLSSLLALLRPALPLILGLSLGCSLSLLRVSWIQGEGEDPCVE  
AVGERGGPQNPDSSARLDQSDDEFKPRIVPYRDPNKPYPKVLRTYIQTGLSRERL  
LVAVLTSRATLSTLAVAVNRTVAHHFPRLLYFTGQRGARAPAGMQVVSHGDERPAWLM

SETLRHLHTHFGADYDWFFIMQDDTYVQAPRLAALAGHLSINQDLYLGRAEEFIGAGEQ  
ARYCHGGFGYLLSRSLLLRLRPHLDGCRGDILSARPDEWLGRCLIDSLGVGCVSQHQG  
QQYRSFELAKNRDPEKEGSSAFLSAFAVHPVSEGLMYRLHKRFSALELERAYSEIEQL  
QAQIRNLTVLTPEGEAGLSWPVGLPAPFTPHSRFEVLGWDYFTEQHTFSCADGAPKCP  
LQGASRADVGDALETALEQLNRRYQPRLRFQKQRLNNGYRRFDPARGMEYTLDLLLEC  
VTQRGHRRALARRVSLLRPLSRVEILPMPYVTEATRVLVPLLVAEAAAAPAFLEAFAA  
NVLEPREHALLTLLLVYGPREGGRGAPDPFLGVKAAAAELERRYPGTRLAWLAVRAEA  
PSQVRLMDVVSKKHPVDTLFFLTWTRPGPEVLNRCRMNAISGWQAFFPVHFQEFNP  
ALSPQRSPPGPPGAGPDPPSPPGADPSRGAPIGGRFDRQASAEGCFYNADYLAARAR  
LAGELAGQEEEEALEGLEVMDFLRFSGHLHFRAVEPGLVQKFSLRDCSPRLSEELYHR  
CRLSNLEGLGGRAQLAMALFEQEQUANST

SEQ ID No:87

MGLLQLLAFSFLALCRARVRAQEPEFSYGCAEGSCYPATGDLLIGRAQKLSVTSTCGLH  
KPEPYCIVSHLQEDKKCFICNSQDPYHETLNPDSHLIENVVTTFAPNRLKIWWQSENGV  
ENVTIQLDLEAEFHFTHLIMTFKTRPAAMLIERSSDFGKTWGVYRYFAYDCEASFPGIS  
TGPMKKVDDIICDSRYSDIEPSTEGEVIFRALDPAFKIEDPYSPIQNLLKITNLRIKFVKLH  
TLGDNLLDSRMEIREKYYYAVYDMVVRGNCFYGHASECAPVDGFFNEEVEGMVHGH  
MCRHNTKGLNCEL CMDFYHDL PWRPAEGRNSNACKKCNENEHSISCHFDMAVYLATG  
NVSGGVCDDCQHNTMGRNCEQCKPFYYQHPERDIRDPNFCERCTCDPAGSQNEGIC  
DSYTDFTGLIAGQCRCKLNVEGEHCDVCKEGFYDLSSDPFGCKSCACNPLGTIPGG  
NPCDSETGHCYCKRLVTGQHCDQCLPEHWGLSNDLDGCRPCDCDLGGALNNSCFAE  
SGQCSCRPHMIGRQCNEVEPGYYFATLDHYLYEAEANLGPVSVIVERQYIQDRIPSW  
TGAGFVRVPEGAYLEFFIDNIPYSMEYDILIRYEPQLPDHWEKAVITVQRPGRIPTSSRC  
GNTIPDDDNQVVSLSPPGSRVVLPRPVCFEKGTNYTVRLELPQYTSSDSDVESPYTLID  
SLVLMPYCKSLDIFTVGGSGDGVVTNSAWETFQRYRCLENSRSVVKTPMTDVCRNIIFS  
ISALLHQTGLACECDPQGSLSVCDPNGGQCQCRPNVVGRTCNRCAPGTFGFGPSGC  
KPCECHLQGSVNAFCNPVTGQCHCFQGVYARQCDCRCLPGHWGFPSCQPCQCNGHA  
DDCDPVTGECLNCQDVTMGHN CERCLAGYYGDPIIGSGDHCRPCPCPDGPD SGRQFA  
RSCYQDPVTLQLACVCDPGYIGSRCDDCASGYFGNPSEVGGSCQPCQCHNNIDTTDP  
EACDKETGRCLKCLYHTEGEHCQFCRFGYYGDALRQDCRKVCVNYLGTVQEHCNGS  
DCQCDKATGQCLCLPNVIGQNCDCR CAPNTWQLASGTGCDPCNCNAAHSFGPSCNEF  
TGQCQCMPGFGGRTCSECQELFWGDPDVECRACDCDPRGIETPQCDQSTGQCVCVE  
GVEGPRCDKCTRGYSGVFPDCTPCHQCFALWDVIIAELTNRTHRFLEKAKALKISGVIG

PYRETVDSVERKVSEIKDILAQSPAAEPLKNIGNLFEEAEKLIKDVTEEMMAQVEVKLSDTT  
SQSNSTAKELDSLQTEAESLDNTVKELAEQLEFIKNSDIRGALDSITKYFQMSLEAEERV  
NASTTEPNSTVEQSALMRDRVEDVMMERESQFKEKQEEQARLLDELAKLQSLDLSAA  
AEMTCGTPPGASCSETECGGPNCRTDEGERKCGGPGCGGLVTVAHNAWQKAMDLD  
QDVL SALAEVEQLSKMVSEAKLRADEAKQSAEDILLKTNATKEKMDKSNEELRNLIKQIR  
NFLTQDSADLDSIEAVANEVLKMEMPSTPQQLQNLTEDIRERVESLSQVEVILQHSAADI  
ARAEMLLEEAKRASKSATDVKVTADMVKEALEEAEKAQVAAEKAQKQADEDIQGTQNL  
TSIESETAASEETLFNASQRISELERNVEELKRKAAQNSGEAEYIEKVVYTVKQSAEDVK  
KTLDGELDEKYKKVENLIAKKTEESADARRKAEMLQNEAKTLLAQANSKLQLLDLERK  
YEDNQRYLEDKAQELARLEGEVRSLLKDISQKVAVYSTCL

SEQ ID No:88

MRGSHRAAPALRPRGRLWPVLAVLAAAAAAGCAQAAMDECTDEGGRPQRCMPEFVN  
AAFNVTVVATNTCGTPPEEYCVQTVGTGVTKSCHLCDAGQPHLQHGAFLTDYNNQA  
DTTWWQSQTMLAGVQYPSSINLT LHLGKAFDITYVRLKFHTSRPESFAIYKRTREDGPW  
IPYQYYSGSCENTYSKANRGFIRTGGDEQQALCTDEFSDFSPLTGGNVAFASTLEGRPS  
AYNFDNSPVLQEWVTATDIRVTLNRLNTFGDEVFNDPKVLKSYYYAISDFAVGGGRCKCN  
GHASECMKNEFDKLV CNCKHNTYGVDCCKLPFFNDRPWRRATAESASECLPCDCNG  
RSQECYFDP ELYRSTGHGGHCTNCQDNTDGAHCERCENFFRLGNNEACSSSCHCSP  
VGSLSTQCDSYGRCSCKPGVMGDKCDRCQPGFHSLTEAGCRPCSCDPSGSGIDE CNV  
ETGRCVCKDNVEGFNCERCKPGFFNLESSNPRGCTPCFCFGHSSVCTNAVGYSVYSIS  
STFQIDEDGWRAEQRDGSEASLEWSSERQDIAVISDSYFPRYFIAPAKFLGKQVLSYGQ  
NLSFSFRVDRRDTRL SAEDLVLEGAGLRVSVPLIAQGNSYPSETTVKYVFRLHEATDYP  
WRPALTPFEFQKLLNNLT SIKIRGTYSERSAGYLDDVTLASARPGPGVPATWVESCTCP  
VGYGGQFC EMCLSGYRRETPNLGPYSPCVLCACNGHSETCDPETGVCNCRDNTAGP  
HCEKCS DGYGDSTAGTSSDCQPCPCPGGSSCAVVPKTKEVVCTNCPTGTTGKRCEL  
CDDGYFGDPLGRNGPVRLCRLCQCSDNIDPNAVGN CNRLTGECLKCIYNTAGFYCDR  
CKDGGFFGNPLAPNPADKCKACNCNPYGTMMKQQSSCNPVTGQCECLPHVTGQDCGAC  
DPGFYNLQSGQGCERCDCALGSTNGQCDIRTGQCECQPGITGQHCERCEVNHFGF  
GPEGCKPCDCHPEGSLSLQCKDDGRCECREGFVGNRCDQCEENYFYNRSWPGCQE  
CPACYRLVKDKVADHRVKLQELES LIANLGTGDEMVTDQAFEDRLKEAEREVMDLLRE  
AQDVKDVDQNLMDRLQRVNNTLSSQISRLQNIRNTIEETGNLAEQARAHVENTERLIEIA  
SRELEKAKVAAANVSVTQPESTGDPNNMTLLAE EARKLAERHKQEADDIVRVAKTAND  
TSTEAYNLLLRTL AGENQTAFEIEELNRKYEQAKNISQDLEKQAARVHEEAKRAGDKAV

EIYASVAQLSPLDSETLENEANNIKMEAENLEQLIDQKLKDYEDLREDMRGKELEVKNLL  
EKGKTEQQTADQLLARADAAKALAEAAKKGRTDLQEANDILNNLKDFDRRVNDNKTA  
AEEALRKIPAINQTITEANEKTREAAQALGSAAADATEAKNKAHEAERIASAVQKNATST  
KAEAERTFAEVTDLNEVNNMLKQLQEAEKELKRKQDDADQDMMMAGMASQAAQEA  
EINARKAKNSVTSLLSIINDLLEQLGQLDVTDLNKLNEIEGTLNKAKDEMKVSDLDRKVSD  
LENEAKKQEAAIMDYNRDIEEIMKDIRNLEDIRKTLPSGCFNTPSIEKP

SEQ ID No:89

MRRAPCVRDKLREIVGASTNWRDHVKAMEERKLLHSFLAKSQDGLPPRRMKDSYIEVL  
LPLGSEPELREKYLTQNTVRFGRILEDLSLGVLCYMHNKIHSKMSPLSIVTALVDKI  
DMCKKSLSPEQDIKFSGHVSWSVGKTSMEVKMQMFQLHGDEFPCVLDATFVMVARDSE  
NKGPAFVNPLIPESPEEEELFRQGELNKGRRIAFSSTSLLKMAPSAEERTTIHEMFLSTL  
DPKTISFRSRVLPSSNAVWMENSKLSLEICHPQERNIFNRIFGGFLMRKAYELAWATAC  
SFGGSRPFVAVDDIMFQKPVEVGSLFLSSQVCFTQNNYIQVRVHSEVASLQEKQHTT  
TNVFHFTFMSEKEVPLVFPKTYGESMLYLDGQRHFNSMSGPATLRKDYLVEP

SEQ ID No:90

MRGSQEVLLMWLLVLAVGGTEHAYRPGRRVCAVRAHGDVPSESFVQRVYQPFLTTCDD  
GHRACSTYRTIYRTAYRRSPGLAPARPRYACCPGWKRTSGLPGACGAAICQPPCRNG  
GSCVQPGRCRCPAGWRGDTCCSDVDECSARRGGCPQRCVNTAGSYWCQCWEGHS  
LSADGTLCPVKGPPRVAPNPTGVDSAMKEEVQRLQSRVDLLEEKQLQLVLAPLHSLAS  
QALEHGLPDPGSLLVHSFQQGLGRIDSLSEQISFLEEQLGSCSCKKDS

SEQ ID No:91

MTLARFVLALMLGALPEVVGFDVSLNDSLHSHRHSPAGPHYPPYYLPTQQRPTTRP  
PPPLPRFPRPPRALPAQRPHALQAGHTPRPHPWGPCPAGEPWVSVTDFGAPCLRWAE  
VPPFLERSPPASWAQLRGQRHNFRCRSPDGAGRPWCFYGDARGKVDWGYCDCRHGS  
VRLRGGKNEFEGTVEVYASGVWGTVCSSHWDDSDASVICHQLQLGGKGIAKQTPFSG  
LGLIPIYWSNVRCRGDEENILLCEKDIWQGGVCPQKMAAAVTCSFSHGPTFPIIRLAGGS  
SVHEGRVELYHAGQWGTVCDDQWDDADAEVICRQLGLSGIAKAHQAYFGEGSGPV  
MLDEVRCCTGNELSIQCPKSSWGEHNCGHKEDAGVSCTPLTDGVIRLAGGKGSHEGR  
LEVYYRGQWGTVCDDGWTELNTYVVCRLGFKYQKQASANHFEESTGPIWLDDVSCS  
GKETRFLQCSRRQWGRHDCSHREDVSIACYPGGEGHRLSLGFPVRLMDGENKKEGR  
VEVFINGQWGTICDDGWTDKDAVICRQLGYKGPARTMAYFGEGKGPIHVDNVKCT

GNERSLADCIKQDIGRHNCRHSEDAGVICDYFGKKASGNSNKESSLSSVCGLRLLHRRQ  
KRIIGGKNSLRGGWPWQVSLRLKSSHGDGRLLCGATLLSSCWVLTAAHCFKRYGNSTR  
SYAVRVGDYHTLVPEEFEEEEIGVQQQIVIHREYRPDRSDYDIALVRLQGPEEQCARFSSH  
VLPACLPLWRERPQKTASNCYITGWGDTGRAYSRTLQQAAPLLPKRFCEERYKGRFT  
GRMLCAGNLHEHKRVDSCQGDSSGGLMCPGESWVVYGVTSWGYGCGVKDSPGV  
YTKVSAFVPWIKSVTKL

SEQ ID No:92

MQKELGIVPSCPGMKSPRPHLLLPLLLLLLLLLLGGAGVPGAWGQAGSLDLQIDEEQPAGT  
LIGDISAGLPAGTAAPLMYFISAEQSGSGVGTDLAIDEHSGVVRTARVLDREQRDRYRFTA  
VTPDGATVEVTVRVADINDHAPAFPQARAALQVPEHTAFGTRYPLEPARDADAGRLGT  
QGYALSGDGAGETFRLETRPGPDGTPVPELVVTGELDRENRSHYMLQLEAYDGGSP  
RRAQALLDVTLDDINDHAPAFNQSRYPHAVVSESLAPGSPVLQVFASDADAGVNGAVTY  
EINRRQSEGDGPFSDAHTGLLQLERPLDFEQRRVHELVVQARDGGAHPELGSFAFTV  
HVRDANDNQPSMTVIFLSADGSPQVSEAAPPQQLVARISVSDPDDGDFAHVNVSL  
EGHFALSTQDSVIYLVCVARRLDREERDAYNLRVTATDSGSPPLRAEAAFLHVTDVND  
NAPAFDRQLYRPEPLPEVALPGSFVVRVTARDPDQGTNGQVTYSLAPGAHTHWFSIDP  
TSGIITTAASLDYELEPQPQLIVVATDGGGLPPLASSATVSVALQDVNDNEPQFQRTFYNA  
SLPEGTQPGTCFLQVTATDADSGPFGLLSYSLGAGLGSSGSPFRIDAHSGDVCTTRL  
DRDQGPSSFDFTVTAVDGGGLKSMVYVKVFLSDENDNPPQFYPREYAASISAQSPPGT  
AVLRLRAHDPDQGSYHILAGNSPPLFTLDEQSGLLTVAWPLARRANSVVQLEIG  
AEDGGGLQAEP SARVDISIVPGTPTPIFEQLQYVFSVPEDVAPGTSVGIVQAHNPPGR  
LAPVTLSLGGDPRGLFSLDAVSGLLQTLRPLDRELLGPVLELEVRAGSGVPPAFAVAR  
VRVLLDDVNDNSPAFPAPEDTVLLPPNTAPGTPIYTLRALPDPSGVNSRVTFLLAGGG  
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LAPRFNSPTYRVLDPSGTTAGTQVLQVQAQAPDGGPITYHLAAEGASSPFGLEPQSGW  
LWVRAALDREAQELYILKVMASGSKAELGQQTGTATVRVSILNQNEHSPRLSEDPTFL  
AVAENQPPGTSVGRVFATDRDSGPNGRLTYSLQQLSEDSKAFRIHPQTGEVTTLQTL  
REQQSSYQLLVQVQDGGSPRSTTGTVHVAVLDLNDNSPTFLQASGAAGGGLPIQVPD  
RVPPGTLVTTLQAKDPDEGENGTILYTLTGPGSELFSLPHSGELLTAAPLIRAERPHYV  
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GSLGSAAPAGVAGALTYTLVGGADPEGTFALDAASGRLYLARPLDFEAGPPWRAL  
TVRAEGPGGAGARLLRVQVQVDENEHAPAFARDPLALALPENPEPGAALYTFRASDA  
DGPGPSNDVRYRLLRQEPVPALRLDARTGALSAPRGLDRETTALLLVEATDRPANA

SRRRAARVSARVFVTDENDNAPVFASPSRVRLPEDQPPGPAALHVVARDPDLGEAAR  
VSYRLASGGDGHFRLHSSTGALS VVRPLDREQRAEHVLT VVASDHGSPPRSATQVLT V  
SVADVND EAPT FQQQEYSVLLRENNPPGTSLLTLRATDPDVGANGQVTYGGVSSSESFS  
LDPDTGVLTTLRALDREEQEEINLT VYAQDRGSPQQLTHVTVRVAVEDENDHAPT FGSA  
HLSLEVPEGQDPQTLTMLRASDPDVGANGQLQYRILDGDP SGAFVLDLASGEFGTMRP  
LDREVEPAFQLRIEARDGGQPALSATLLLTVTVLDANDHAPAFPVPAYSVEVPEDVPAG  
TLLLQLQAHPDAGANGHVTYL GAGTAGAFLLEPSSGELRTAAALDREQCPSYTF SV  
SAVDGAAAGPLSTTVSVTITVRDVNDHAPT FPTSPLRLRLPRPGPSFSTPTLALATLRAE  
DRDAGANASILYRLAGTPPPGTTVDSYTGEIRVARSPVALGPRDRVLFIVATDLGRPARS  
ATGVII VGLQGEAERGPRFPRASSEATIRENAPPGTPIVSPRAVHAGGTNGPITYSILSGN  
EKGTF SIQPSTGAITVRS AEGLDFEVSPRLRLVLQAESGGAF AFTVLT LTLQDANDNAPR  
FLRPHYVAFLPESRPLEGPLLQVEADDLDQSGGGQISYSLAASQPARGLFHVDPTTGTI  
TTTAILDREIWAETRLVLMATDRGSPALVGSATLTVMVIDTNDNRPTIPQPWELRVSEDA  
LLGSEIAQVTGNDVDSGPVLWYVLSPSGPQDPFSVGRYGGRVSLTGPLDFEQCDRYQ  
LQLLAHDGPHEGRANLTVLVEDVNDNAPAFS QSLYQVM LLEHTPPGSAILSVSATDRDS  
GANGHISYHLASPADGFSVDPNNGTLFTIVGTVALGHDGSGAVDVVLEARDHGAPGRA  
ARATVHVQLQDQNDHAPSFTLSHYRVAVTEDLPPGSTLLTLEATDADGSRSHA AVDYSI  
ISGNWGRVFQLEPRLAEAGESAGPGPRALGCLVLLEPLDFESLTQYNLTVA AADRGGQP  
PQSSVVPVTVTVLDVNDNPPVFTRASYRVTVPEDTPVGAELLHVEASDADPGPHGLVR  
FTVSSGDPSGLFELDESSGTLRLAHALDCETQARHQLVVQAADPAGAHFALAPVTIEVQ  
DVNDHGPAFPLNLLSTVAENQPPGTLVTTLHAIDGDAGAFGRLRYSLLEAGPGPEGRE  
AFALNSSTGELRARVPFDYEHTESFRLLVGAADAGNLSASVTVSVLVTGEDEYDPVFLA  
PAFH FQVPEGARRGHS LGHVQATDEDGGADGLVLYSLATSSPYFGINQTTGALYLRVD  
SRAPGSGTATSGGGGRTRREAPRELRLLEVIARGPLPGSRSATVPVTVDITHALGLAPD  
LNLLL VGAVAASLGVVVVLALALVLGLVRARSRKAEAAPGPMSQAAPLASDSLQKLGR  
EPPSPPPSEHLYHQTLPSYGGPGAGGPYPRGGS LDPSHSSGRGSAEAAEDDEIRMINE  
FPRVASVASSLAARGPDSGIQQDADGLSDTSCEPPAPDTWYKGRKAGLLLPGAGATLY  
REEGPPATATAFLGGCGLSPAPTGDYGF PADGKPCVAGALTAIVAGEEELRGSYNWDY  
LLSWCPQFQPLASVFTEIARLKDEARPCPPAPRIDPPPLITAVAH PGAKSVPPKPANTAA  
ARAI FPPASHRSPISHEGSLSSAAMSPSFSPSLSPLAARSPVVSPFGVAQG GPSASALSA  
ESGLEPPDDTELHI

MRPLLLLALLGWLLLAELAKGDAKPEDNLLVLT VATKETEGFRRFKRSAQFFNYKIQALGL  
GEDWNVEKGTSAGGGQKVRLLKKALEKHADKEDLVILFTDSYDVL FASGPRELLKKFR  
QARSQVVFSAEELIYPDRRLET KYPVVS DGKRFLGSGGFIGYAPNLSKLVAEWEGQDS  
DSDQLFYTKIFLDPEKREQINITLDHRCRIFQNL DGALDEVVLKFEMGHVRARNLAYDTL  
PVLHNGNGPTKLQLNYLGNYPFWTFETGCTVCDEGLRSLKGIGDEALPTVLVGVFIEQ  
PTPFVSLFFQRLRLHYPQKHMRLFIHNHEQHKAQVEEFLAQHGSEYQSVKLVGPEV  
RMANADARNMGADLCRQDRSCTYYFSVDADVALTEPN SLRLLIQQNKNVIAPLMTRHG  
RLWSNFWGALSADGYYARSEDYVDIVQGRRVGVWNVPYISNIYLIKGSALRGELQSSD  
LFHHSKLDPDMAFCANIRQQDVFMFLTNRHTLGHLLSLDSYRTTHLHNDLWEVFSNPE  
DWKEYIHQNYTKALAGKLVETPCPDVYWFPIFTEVACDELVEEMEHFGQWSLGNNKD  
NRIQGGYENVPTIDIHMNQIGFEREWHKFLLEYIAPMTEKLYPGYYTRAQFDLAFVVRYK  
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THYHEGLPTTRGTRYIAVSFVDP

SEQ ID No:94

MTSSGPGPRFLLLLPLLLPPAASASDRPRGRDPVNPEKLLVITVATAETEGYL RFLRSAE  
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AGSPTELLKKFVQSGSRLLFSAESFCWPEWGLAEQYPEVGTGKRFLNSGGFIGFATTIH  
QIVRQWKYKDDDDDDQLFYTRL YLDPGLREKLSLNL DHKSRIFQNLNGALDEVVLKFDRN  
RVRIRNVAYDTLP IVVHGNGPTKLQLNYLGNYPNGWTPEGGCGFCNQDRRTLPGGQ  
PPPRVFLAVFEQPTPFLPRFLQRLLLLDYPPDRVTLFLHNNEVFHEPHIADSWPQLQD  
HFSAVKLVGP EEALSPGEARDMAMDLCRQDPECEFYFSLDADAVLTNLQTLRILIEENR  
KVIAPMLSRHGKLWSNFWGALSPDEYYARSEDYVELVQRKRVGVWNVPYISQAYVIRG  
DTLRMELPQRDV FSGSDTDPMAFCKSFRDKGIFLHLSNQHEFG RLLATSRYDTEHLH  
PDLWQIFDNPVDWKEQYIHENYSRALEGE GIVEQPCPDVYWFPLLSEQMCDELVAEME  
HYGQWSGGRHEDSRLAGGYENVPTVDIHMKQVGYEDQWLQLLRTYVGPMTESLFPG  
YHTKARAVMNFVVRYRPDEQPSLRPHHDSSTFTLNVALNHKGLDYE GGGCRFLRYDC  
VISSPRKGWALLHPGRLTHYHEGLPTTWGTRYIMVSFVDP

SEQ ID No:95

MAACTARRPLAVGSRWWSRSLTGARWPKPLCAAAGAGAFSPASTTTTTRRHLSSRNRP  
EGKVLETVG VFEVPKQNGKYETGQLFLHSIFGYRGVVLFPWQARLYDRDVASAAPEKA  
ENPAGHGSKEVKGKTHTY YQVLIDARDCPHISQRSQTEAVTFLANHDDSRALYAIPGLD  
YVSHEDILPYTSTDQVPIQHELPERFLLYDQTKAPPFVARETLRAWQEKNHPWLELSDV



HRETTENIRVTVIPFYMGMREAQNSHVYWWRYCIRLENLDSDVVQLRERHWRIFSLSG  
TLETVRGRGVVGREPVLSKEQPAFQYSSHVSLQASSGHMWGTFRFERPDGSHFDVRI  
PPFSLESNKDEKTPPSGLHW

SEQ ID No:96

METIWIYQFRLIVIGDSTVGKSCLLHRFTQGRFPGLRSPACDPTVGVDFFSRLLIEIPGK  
RIKLQLWDTAGQERFRSITRSYYRNSVGGFLVFDITNRRSFEHVKDWLEEKMYVQPF  
RIVFLLVGHKCDLASQRQVTRREEAEKLSADCGMKYIETSAKDATNVEESFTILTRDIYELI  
KKGEICIQDGWEGVKSGFVPNTVHSSEEAVKPRKECFC

SEQ ID No:97

MERSGWARQTFLALLLGATLRARAAAGYYPRFSPFFFLCTHHGELEGDGEQGEVLISL  
HIAGNPTYYPGQEYHVTISTSTFFDGLLVTGLYTSTSVQASQSIGGSSAFGFGIMSDHQ  
FGNQFMCSVVASHVSHLPTTNLSFIWIAPPAGTGCVNFMATATHRGQVIFKDALAQQLC  
EQGAPTDVTVHPLAEIHSDSIILRDDFDSYHQLQLNPNIWVECNCETGEQCGAIMHG  
NAVTFCEPYGPRELITTGLNTTTASVLQFSIGSGSCRFSYSDPSIIVLYAKNNSADWIQLE  
KIRAPSNVSTIIHILYPEDAKGENVQFQWKQENLRVGEVYEACWALDNILIINSAHRQVV  
LEDSLDPVDTGNWLFFPGATVKHSCQSDGNSIYFHGNEGSEFNFATTRDVDLSTEDIQ  
EQWSEEFESQPTGWDVLGAVIGTECGTIESGLSMVFLKDGERKLCTPSMDTTGYGNLR  
FYFVMGGICDPGNSHENDIILYAKIEGRKEHITLDTLSYSSYKVPSLVSVVINPELQTPATK  
FCLRQKNHQGHNRNVWAVDFFHVLPVLPSTMSHMIQFSINLGCGTHQPGNSVSLEFST  
NHGRSWSLLHTECLPEICAGPHLPHSTVYSSENYSGWNRITIPNAAALTRNTRIRWRQ  
TGPILGNMWAIDNVYIGPSCLKFCSGRGQCTRHGCKCDPGFSGPACEMASQTFPMFIS  
ESFGSSRLSSYHNFYSIRGAEVSFSGCVLASGKALVFNKEGRRQLITSFLDSSQSRFLQ  
FTLRLGSKSVLSTCRAPDQPGEGVLLHYSYDNGITWKLLEHYSYLSYHEPRIISVELPGD  
AKQFGIQFRWWQPYHSSQREDVWAIDEIIMTSVLFNSISLDFTNLVEVTQSLGFYLGNV  
QPYCGHDWTLCTFTGDSKLASSMRYVETQSMQIGASYMIQFSLVMGCGQKYTPHMDN  
QVKLEYSTNHGLTWHLVQEECLPSMPSCQEFTSASIYHASEFTQWRRVIVLLPQKTWS  
SATRFRWSQSYYTAQDEWALDSIYIGQQCPNMCSGHGS CDHGICRCDQGYQGTECH  
PEAALPSTIMSDFENQNGWESDWQEVIIGGEIVKPEQGGCVISSGSSLYFSKAGKRQLV  
SWDLDTSWVDFVQFYIQIGGESASCNKPDSREEGVLLQYSNNGGIQWHLLAEMYFSDF  
SKPRFVYLELPAAAKTPCTFRFRWWQPVFSGEDYDQWAVDDIILSEKQKQIIPVINPTLP  
QNFYEKPAFDYPMNQMSVWLMLANEGMVKNETFCAATPSAMIFGKSDGDRFAVTRDL  
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RELSEPTMYHTGDFFEWTRITIVIPRSLASSKTRFRWQIQUSSSQKNVPPFGLDGVYISEP  
 CPSYCSGHGDCISGVCFCDLGYTAAQGTCTVSNVPHNEMFDRFEGKLSPLWYKITGA  
 QVGTGCGTLNDGKSIFYNGPGKREARTVPLDTRNIRLVQFYIQIGSKTSGITCIKPRTRN  
 EGLIVQYSNDNGILWHLLRELDFFMSFLEPQIISIDLPQDAKTPATAFRWWQPQHGHKHA  
 QWALDDVLIGMNDSSQTGFQDKFDGSLDLQANWYRIQGGQVDIDCLSMDETALIFTENIG  
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 SSSHVSSLCSTEHHPSSTYYAGTMQGWRRREVVFHFGKLHLCGSRFRWYQGFYPAGS  
 QPVTWADNVYIGPQCEEMCNGQGSCINGTKCICDPGYSGPTCKISTKNPDLKDDFEG  
 QLESDRFLMSGGKPSRKCGILSSGNLFFNEDGLRMLMTRDLDSLHARFVQFFMRLG  
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 VRDCLPTNVECSRYHLQRILVSDTFNKWTRITLPLPYTRSQAATFRFRWHQAPFDKQQ  
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 PSSQNWLTVNGGKLSTVCGAVASGMALHFSGGCSRLLVTVDLNLNAEFIQFYFMYGC  
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 RHDGLDQNDWAIDNVLISGSADQRTVMLDTFSSAPVPQHERSPADAGPVGRIAFDMFM  
 EDKTSVNEHWLFHDDCTVERFCDSPDGVMLCGSHDGREVYAVTHDLTPTEGWIMQFK  
 ISVGCKVSEKIAQNIHVQYSTDFGVSWNYLVPQCLPADPKCSGSVSQPSVFFPTKGW  
 KRITYPLPESLVGNPVRFRFYQKYSMDQWADNFYLGPGCLDNCRGHGDCLREQCICD  
 PGYSGPNCYLTHTLKTLKERFDSEEIKPDLWMSLEGGSTCTECGILAEDTALYFGGST  
 VRQAVTQDLDLRGAKFLQYWGRIGSENNMTSCHRPICRKEGVLLDYSTDGGITWTLH  
 EMDYQKYISVRHDYILLPEDALTNTTRLRWWQPFVISNGIVVSGVERAQWALDNILIGGA  
 EINPSQLVDTFDDEGTSHEENWSFYFNAVRTAGFCGNPSFHLWPNKKKDKTHNALSS  
 RELIIQPGYMMQFKIVVGCEATSCGDLHSMLEYTKDARSWSQLVQTQCLPSSSNSIG  
 CSPFQFHEATYNSVNSSSWKRITIQLPDHVSSSATQFRWIKGEETEKQSWAIDHVIYIG  
 EACPKLCSGHGYCTTGAICICDESFGDDCSVFSHDLPSYIKDNFESARVTEANWETIQ  
 GGVIGSGCGLAPYAHGDSLYFNGCQIRQAATKPLDLTRASKIMFVLQIGSMSQTDSCN

SDLSGPHAVDKAVLLQYSVNNGITWHVIAQHQPDKFTQAQRVSYNVPLEARMKGVLLR  
WWQPRHNGTGHDQWALDHVEVVLVSTRKQNYMMNFSRQHGLRHFYNRRRRSLRRY  
P

SEQ ID No:98

MARVAWGLLWLLLGSAGAQYEKYSFRGFPPEDLMPLAAAYGHALEQYEGESWRESAR  
YLEAALRLHRLLRDSEAFCHANCSGPAPAAKPPDPDGGRADEWACELRLFGRVLERAAC  
LRRCKRTLPAFQVPYPPRQLLRDFQSRLPYQYLHYALFKANRLEKAVAAAYTFLQRNPK  
HELTAKYLNYYQGMLDVADES LTDLEAQPYEAVFLRAVKLYNSGDFRSSTEDMERALS  
EYLAVFARCLAGCEGAHEQVDFKDFYPAIADLFAESLQCKVDCEANLTPNVGGYFVDKF  
VATMYHYLQFAYYKLNDVRQAARSAASYMLFDPKDSVMQQNLVYYRFHRARWGLEEE  
DFQPREEAMLYHNQTAELRELLEFTHMYLQSDDEMELEETEPPEPEDALSDAEFEGE  
GDYEEGMYADWWQEPDAKGDEAEAEPEPELA

SEQ ID No:99

MQSRLLLLGAPGGLGDVASRRVRLLLLRQVLRGRPGGDQQRLEVRLHSGATDSGETV  
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SVAMQYLELTKREVEYIALSRDTTETDLKQRREIRAGTAFYIDQCAVRAATEGRTLVLG  
LEKAERNVLPVLNNLLENREMQLEDGRFLMSAERYDKLLQDHTKEELDAWKIVRVSEN  
FRVIALGLPVPRYSGNPLDPPLRSRFQARDIYFLPFQDQLKLLYSVGANVSAEKISQLLS  
FATTLCSESSTLGLPDFPLDSLPEAVQILDSFPMMSIEHALQWVYPYTLGGHEGKMA  
VEGVLRFEELQGSGHSLLPKEIVRVERMTDSHGSYAHVTIRVAGKEVTIKVPAGTRAVN  
QPCAPDHFIQTVSHKQLLAEMVQSHMVKDICLIGGKGCCKTVIAKNFAALLGYSIEPIML  
YQDMTARDLLQQRYTLPNGDTAWRSSPLVSAAREGKLVLLDGIHRVNAGTLAVLQRLIH  
DRELSLYDGSRLREDRYLSLKERLQLTDEQLQNRSIFPIHPSFRIIALAEPPIVGSTTQQ  
WLGPEFLTMFFFHHMKPLVKSEEIQVIKETVPNPVQEALEKLLSVTHKLRETQDPTAQL  
AASLSTRQLLRISRRLSKYPSENLDHDAITKACLSRFLPSLAQSALEKNLADAAIETNTEDS  
LEPELENYKCKVVAGSLKIGAVSVPVHNAHEKMKVPDVLFYDNVQHMVVMEDMLKDFV  
LGEHLLLVGNQGVGKNKIVDRFLHLLNRPREYIQLHRDTTVQSLTLQPTVKGGILVYEDS  
PLVKAVKLGHILVVDEADKAPTNVTCILKTLVENGEMILADGRRIVADAANVDGRENLIAI  
HPDFRMLALANRPGFPFLGNDFFGTLDIFSCHADNPKPHSELSMLKQYGPDPVPEPVL  
QKLVAAFGELRNADQGIINYPYSTREVVNIVKHLQKFPTGLSSVVRNVFDFDSYNND  
MREILMNTLHKYGIPIGAKPTNVQLAKE

SEQ ID No:100

MNLILEFLLLVGVIISYLESLVKFFIPRRRKSVTGQTVLITGAGHGIGRLTAYEFAKQKSR  
LVLWDINKRGVEETADKCRKLGAVVHVFFVDCSNRAEIYNSVDQVKREVG DVEIVVNNA  
GAIYPADLLSAKDEEITKTFEVNILGHFWIIKALLPSMLRRNSGHIVTVASVCGHGVIPYLIP  
YCSSKFAAVGFHRLTAELDTLGKTGIKTSC LCPVFVNTGFTKNPSTRLWPVLEPEEVA  
RSLINGILTNNKMIFVPSYINIFLILEKGGPGFSSKHPHGGSSQQPVTPIPGDLTPSSDFLKH

SEQ ID No:101

MNTSQVEALGIQMLPGYRDPYHGRPLTKGELGCFLSHYNIWKEVVDRGPQKSLVFEDD  
LRFEIFFKRRLMNLMRDVEREGLDWDLIYVGRKRMQVEHPEKAVPRVRNLVEADYSYW  
TLAYVISLQGARKLLAAEPLSKMLPVDEFLPVMFDKHPVSEYKAHFSLRNLHAFSVEPLLI  
YPTHYTGDDGYVSDTETS VVWNNEHVKTDWDRAKSQKMREQQALSREAKNSDVLQS  
PLDSAARDEL

SEQ ID No:102

MAPAKATNVVRLLLGSTALWLSQLGSGTVAASKSVTAHLAAKWPETPLLLEASEFMAEE  
SNEKFWQFLETVQELAIYKQTESDYSYNNLILKKAGQFLDNLHINLLKFAFSIRAYSPAIQ  
MFQQIAADEPPPDGCNAFVVIHKKHTCKINEIKLLKKAASRTRPYLFKGDHKKFPTNKEN  
LPVVILYAEMGTRTFSAFHKVLSEKAQNEEILYVLRHYIQKPSSRKMYLSGYGVELAIKST  
EYKALDDTQVKTVTNTTVEDETETNEVQGFLFGKLKEIYSDLRDNLTA FQKYLIESNKQM  
MPLK VWELQDLSFQAASQIMSTPVYDAIKLMKDISQNFPIKARSLTRIAVNQHMREEIKE  
NQKDLQVRFKIQPGDARLFINGLRVDM DVYDAFSILDMLKLEGKMMNGLRNLGINGED  
MSKFLKLNSHIWEYTYVLDIRHSSIMWINDLEND DLYITWPTSCQKLLKPVFPGSVPSIRR  
NFHNLVLFIDPAQEYTLDFIKLADV FYSHEVPLRIGFVFILNTDDEVDGANDAGVALWRAF  
NYIAEEFDISEAFISIVHMYQKVKKDQNILTVDNVKS V LQNTFPHANIWDILGIHSKYDEER  
KAGASFYKMTGLGPLPQALYNGEPFKHEEMNIKELKMAVLQRMMDASVYLQREVFLGT  
LNDRTNAIDFLMDRNNVVPRINTLILRTNQQYLNLISTSVTADVEDFSTFFFLDSQDKSAV  
IAKNMYYLTQDDESIISAVTLWIIADFDKPSGRKLLFNALKHMKTSVHSRLGIYNPTSKIN  
EENTAI SRGILAAFLTQKNMFLRSFLGQLAKEE IATTIYSGDKIKTFLIEGMDKNAFEKKYN  
TVGVNIFRTHQLFCQDVLKLRPGEMGIVSNGRFLGPLDEDFYAEDFY LLEKITFSNLGEK  
IKGIVENMGINANNMSDFIMKVDALMSSVPKRASRYDVTF LRENHSHVIKTNPQENDMFF  
NVIAIVDPLTREAQKMAQLLVVLGKIINLKIKLFMNCRGRLSEAPLESFYRFVLEPELMSG  
ANDVSSLGPVAKFLDIPESPL LILNMITPEGWL VETVHSNCDLDNIHLKDTEKTVTAEYEL  
EYLLLEGQC FDKVTEQPPRGLQFTLGTKNKPAVVDTIVMAHHGYFQLKANPGAWILRLH

QGKSEDIYQIVGHEGTDSQADLEDIIVVLNSFKSKILKVKKETDKIKEDILTDEDEKTKG  
LWDSIKSFTVSLHKENKKEKDVLNIFSVASGHLYERFLRIMMLSVLRNTKTPVKFWLLKN  
YLSPTFKEVIPHMAKEYGFYELVQYRWPRWLRQQTERQRIIWGYKILFLDVLFPPLAVD  
KIIFVDADQIVRHDLKELRDFDLGAPYGYTPFCDSRREMDGYRFWKTGYWASHLLRR  
KYHISALYVVDLKKFRRIGAGDRLRSQYQALSQDPNSLSNLDQDLPNNMIYQVAIKSLPQ  
DWLWCETWCDDSKQRAKTIDLCNNPKTKESKLKAAARIVPEWVEYDAEIRQLLDHLE  
NKKQDTILTHDEL

SEQ ID No:103

MADKVRRRQRPRRRVCWALVAVLLADLLALSDTLAVMSVDLGSESMKVAIVKPGVPMEI  
VLNKESSRRKTPVIVTLKENERFFGDSAASMAIKNPATLRYFQHLLGKQADNPHVALYQ  
ARFPEHELTDPQRQTVHFQISSQLQFSPEEVLGMVLNYSRSLAEDFAEQPIKDAVITVP  
VFFNQAERRAVLQAARMAGLKVQLINDNTATALSYGVFRRKDINTTAQNIMFYDMGSG  
STVCTIVTYQMVKTKKEAGMQPQLQIRGVGFDRTLGGLEMELELRERLAGLFNEQRKGQ  
RAKDVRENPRAMAKLLREANRLKTVLSANADHMAQIEGLMDDVDFKAKVTRVEFEELC  
ADLFERVPGPVQQALQSAEMSLDEIEQVILVGGATRVPRVQEVLLKAVGKEELGKNINA  
DEAAAMGAVYQAAALSKAFKVKPFVVRDAVVYPILVEFTREVEEEEPGIHSLKHNRVLF  
SRMGYPYPQRKVITFNRYSHDFNFHINYGDLGFLGPEDLRVFGSQNLTTVKLKGVGDSF  
KKYPDYESKGIAHFNLDESGVLSLDRVESVFETLVEDSAEEESTLTKLGNTISSLFGGG  
TTPDAKENGTDTVQEEEESPAEGSKDEPGEQVELKEEAEAPVEDGSQPPPPPEPKGDA  
TPEGEKATEKENGDKSEAQKPSEKAEAGPEGVAPAPEGEKKQKPARKRRMVEEIGVEL  
VVLDPDLPEDKLAQSVQKLQDLTLRDLEKQEREKAANSLEAFIFETQDKLYQPEYQEV  
STEEQREEISGKLSAASTWLEDEGVGATTVMLEKLAELRKLCQGLFFRVEERKKWPE  
RLSALDNLLNHSSMFLKGARLIPEMDQIFTEVEMTTLEKVINETWAWKNATLAEQAKLPA  
TEKPVLLSKDIEAKMMALDREVQYLLNKAKFTKPRPRPKDKNGTRAEPPLNASASDQG  
EKVIPPAGQTEDAEPISEPEKVETGSEPGDTEPLELGGPGAEPQKEQSTGQKRPLKN  
DEL

SEQ ID No:104

LVRLPDSSGGRRSLVSQVAVHGENGRGGLGCVRAIQCLVPSYSPRPRSSMFTRAQV  
RRILQRVPGKQRFGIYRFLPFFFVLGGTMEWIMIKVRVGGQETFYDVYRRKASERQYQRR  
LEDE

SEQ ID No:105

MSNGYEDHMAEDCRGDIGRTNLIVNYLPQNMTQDELRSLSFSSIGEVEESAKLIRDKVAGH  
SLGYGFVNYVTAKDAERAINTLNGRLQSKTIKVSYPSPSEVIKDANLYISGLPRTMTQ  
KDVEDMFSRFGRIINSRVLVDQTTGLSRGVAFIRFDKRSEAEAAITSFNHGKPPGSSEPI  
TVKFAANPNQKNVALLSQLYHSPARRFGGPVHHQAQRFRFSPMGVDHMSGLSGVNV  
PGNASSGWCIFIYNLGQDADEGILWQMFGPFGAVTNVKVIRDFNTNKCKGFGFVTMTN  
YEEAAMAIASLNGYRLGDKILQVSFKTNKSHK

SEQ ID No:106

MRDRLPDLTACRKNDDGDTVVVVEKDHFMDDFFHQVEEIRNSIDKITQYVEEVKKNHSII  
LSAPNPEGKIKEELEDLNKEIKKTANKIAAKLKAIEQSFDQDESGNRTSVDLRIRRTQHSV  
LSRKFEAMAEYNEAQTLFRERSKGRIQRQLEITGRTTTDDELEEMLESGKPSIFTSDIIS  
DSQITRQALNEIESRHKDIMKLETSIRELHEMFMDMAMFVETQGEMINNIERNVMNATD  
YVEHAKEETKKAICYQSKARRKKWIIIAVSVVLVVIIVLIIGLSVGK

SEQ ID No:107

MYREWVVNVFMMLYVQLVQGSSNEHGPVKRSSQSTLERSEQQIRAASSLEELLRITH  
SEDWKLWRCRLRLKSFTSMDSRSASHRSTRFAATFYDIETLKVIDEEWQRTQCSPRET  
CVEVASELGKSTNTFFKPPCVNVFRCGGCCNEESLICMNTSTSYISKQLFEISVPLTSVP  
ELVPVKVANHTGCKCLPTAPRHPYSIIRRSIQIPEEDRCSHSHKKLCPIDMLWDSNKCKCV  
LQEENPLAGTEDHSHLQEPALCGPHMMFDEDRCECVCKTPCPKDLIQHPKNCSCFEC  
KESLETCCQKHKLFPDTCSCEDRCPFHTRPCASGKTACAKHCRFPKEKRAAQGPHS  
RKNP

SEQ ID No:108

MMNNSGYSDAGLGLGDETDEMPSTEKDLAEDAPWKKIQQNTFTRWCNEHLKCVGKRL  
TDLQRDLSDGLRLIALLEVLSQLRMYRKHFHPRPNFRQMKLENVSVALEFLEREHIKLVSI  
DSKAIVDGNLKLILGLIWTILHYSISMPMWEDEDEDARKQTPKQRLLGWIQNKVPQLPI  
TNFNRDWQDGKALGALVDNCAPGLCPDWEAWDPNQPVENAREAMQQADDWLGVQP  
VIAPEEIVDPNVDEHSVMTYLSQFPKAKLKPGAPVRSKQLNPKKAIAYGPGIEPQGNTVL  
QPAHFTVQTVDAGVGEVLVYIEDPEGHTEEAKVVPNNDKDRTYAVSYVPKVAGLHKVT  
VLFAGQNIERSPFENVGMALGDANKVSARGPGLEPVGNVANKPTYFDIYTAGAGTGD  
VAVVIVDPQGRRTVEVALEDKGDSTFRCTYRPAMEGPHTVHVAFAGAPITRSPFPVH  
VSEACNPACRASGRGLQPKGVRVKEVADFKVFTKGAGSGELKVTVKGPKGTEEPVK  
VREAGDGVFECEYYPVVPGKYVVTITWGGYAI PRSPFEVQVSPEAGVQKVRAWGPGL

ETGQVGKSADFFVEAIGTEVGTGLGFSIEGPSQAKIECDDKGDGSCDVRYWPTEPGEYA  
 VHVICDDEDIRDSPFIAHILPAPPDCFPDKVKAFGPGLEPTGCIVDKPAEFTIDARAAGKG  
 DLKLYAQDADGCPIDIKVIPNGDGTFRCSYVPTKPIKHTIIISWGGVNVPKSPFRVNVGEG  
 SHPERVKVYGPVGVEKTGLKANEPYFTVDCSEAGQGDSIGIKCAPGVVGPAAEADIDFD  
 IIKNDNDTFTVKYTPPGAGRYTIMVLFANQEIPASPFHIKVDPSHDASKVKAEGPGLNRT  
 GVEVGKPTHFTVLTKGAGKAKLDVQFAGTAKGEVVRDFEIIDNHDYSYTVKYTAVQQG  
 NMAVTVTYGGDPVPKSPFVNVNAPPLDLISKIKVQGLNSKVAVGQEQAFSVNTRGAGG  
 QGQLDVRMTSPSRRPIPCKLEPGGGAEAAQAVRYMPPEEGPYKVDITYDGHVPVPGSPF  
 AVEGVLPPDPSKVCAYGPGLKGGVLGTPAPFSIDTKGAGTGGLGLTVEGPCEAKIECQ  
 DNGDGSCAVSYLPTEPGEYTINILFAEAHIPGSPFKATIRPVFDPSKVRASGPGLERGKV  
 GEATFTVDCSEAGEAELTIEILSDAGVKAEVLIHNNADGTYHITYSPAFFPGTYTITIKYGG  
 HPVPKFPTRVHVQPAVDTSGVKVSGPGVEPHGVLREVTTFTVDARSLTATGGNHVTA  
 RVLNPSGAKTDTYVTDNGDGTYRVQYTAYEEGVHLVEVLYDEVAVPKSPFRVGVTEGC  
 DPTRVRAFGPGLEGGLVNKANRFTVETRAGAGTGGLGLAIEGPSEAKMSCKDNKDGSC  
 TVEYIPFTPGDYDVNITFGGRPIPGSPFRVPVKDVVDPGKVKCSGPGLGAGVRARVPQT  
 FTVDCSQAGRAPLQVAVLGPTGVAEPVEVRDNGDGTHTVHYTPATDGPYTVAVKYAD  
 QEVPRSPFKIKVLPAMDASKVRASGPGLNASGIPASLPVEFTIDARDAGEGLLTVQILED  
 PEGKPKKANIRDNGDGTYTVSYLPDMSGRYTITIKYGGDEIPYSPFRIHALPTGDASKCL  
 VTVSIGGHGLGACLGPRIQIGQETVITVDAKAAGEGKVTCTVSTPDGAELDVDVVENHD  
 GTFDIYYTAPEPGKYVITIRFGGEHIPNSPFHVLACDPLPHEEEPSEVPQLRQPYAPPRP  
 GARPTHWATEEPVVPVEPMESMLRPFNLVIPFAVQKGELTGEVRMPSGKTARNITDN  
 KDGTITVRYAPTEKGLHQMGIKYDGNHIPSPLQFYVDAINSRRHVSAYGPGLSHGMVNK  
 PATFTIVTKDAGEGGLSLAVEGPSKAEITCKDNKDGTCTVSYLPAPGDYSIIVRFDDKHI  
 PGSPFTAKITGDDSMRTSQLNVGTSTDVSLKITESDLSQLTASIRAPSGNEEPCLLKRLP  
 NRHIGISFTPKEVGEHVSVRKSGKHVTNSPFKILVGPSEIGDASKVRVWGKGLSEGHT  
 FQVAEFIVDTRNAGYGGLGLSIEGPSKVDINCEMEDGTCKVTYCPTEPGTYIINIKFADK  
 HVPGPSFTVKVTGEGRMKESITRRRQAPSIATIGSTCDLNLKIPGNWFQMVSAQERLTR  
 TFTRSSHTYTRTERTEISKTRGGETKREVRVEESTQVGGDPFPAVFGDFLGRERLGSF  
 GSITRQQEAGEASSQDMTAQVTSPSGKVEAAEIVEGEDSAYSVRFPQEMGPHTVAVKY  
 RGQHVPGSPFQFTVGPLGEGGAHKVRAGGTGLERGVAGVPAEFSIW TREAGAGGLSI  
 AVEGPSKAEIAFEDRKDGSCGVSYVVQEPGDYEVSIFNDEHIPDSPFVVPVASLSDDA  
 RRLTVTSLQETGLKVNQPASFAVQLNGARGVIDARVHTPSGAVEECYVSELDSDKHTIR  
 FIPHENGVSIDVKFNGAHIPGSPFKIRVGEQSQAGDPGLVSAYGPGLEGGTGVSSEFI  
 VNTLNAGSGALSVTIDGPSKVQLDCRECPEGHVVITYTPMAPGNYLIAIKYGGPQHIVGS

PFKAKVTGPRLSGGHS�HETSTVLVETVTKSSSSSRGSSSYSSIPKFSSDASKVVTRGPGL  
SQAQFVGQKNSFTVDCSKAGTNMMMVGVLHGPKTPCEEVYVKHMGNRVYNVTYTVKEK  
GDYILIVKWGDESVPGSPFKVKVP

SEQ ID No:109

MDGASAEQDGLQEDRSHSGPSSLPEAPLKPPGPLVPPDQQDKVQCAEVNRASLEGES  
PDGPGQGGGLCQNGPTPPFPDPPSSLDPTTSPVGPDPASPGVAGFHDNLRKSQGTSAEG  
SVRKEALQSLRLSLPMQETQLCSTDSPLEKEEQVRLQARKWLEEQLKQYRVKRQQE  
RSSQPATKTRLFSTLDPELMLNPENLPRASTLAMTKEYSFLRTSVPRGPKVGSGLPAH  
PREKKTSSKIRSLADYRTEDSNAGNSGGNVPAPDSTKGS�KQNRSSAASVVSEISLS  
PDTDDRLENTSLAGDSVSEVDGNDSDSSSYSSASTRGTYGILSKTVGTQDTPYMVNGQ  
EIPADTLGQFPSIKDVLQAAAAEHQDQGGQEVNGEVRSRRDSICSSVSLESSAAETQEEM  
LQVLKEKMRLEGQLEALSLEASQALKEKAELQAQLAALSTKLQAQVECSHSSQQRQDS  
LSSEVDTLKQSCWDLERAMTDLQNMLEAKNASLASSNNDLQVAEEQYQRLMAKVEDM  
QRSMLSKDNTVHDLRQQMTALQSQLQQVQLERTTTLTSKLKASQAEISSLQSVRQWYQ  
QQALAAQEARVRLQGEMAHIQVGQMTQAGILEHLKLENVSLSQQLTETQHRSMEKEGR  
IAAQLQGIEADMLDQEA AFMQIQEAKTMVEEDLQRRLEEFEGERERLQRMADSAASLE  
QQLEQVKLTLLQRDQQLEALQQEHLDLMKQLTLTQEALQSREQSLDALQTHYDELQAR  
LGELQGEAASREDTICLLQNEKIILEAALQAAKSGKEELDRGARRLEEGTEETSETLEKL  
REELAISKSGQVEHLQQETAALKKQMQKIQEQLQKVMVEAYRRDATSKDQLISELKAT  
RKRLDSELKELRQELMQVHGKRTAEAELSRLHREVAQVRQHMADEGLHLSAQKER  
DEMETHLQSLQFDKEQMVAVTEANEALKKQIEELQQEARKAITEQKQKMRRLGSDLTS  
AQKEMKTKHKAYENAVGILSRRLQEALAAKEAADAELGQLRAQGGSSDSSLALHERIQA  
LEAELQAVSHSKTLLEKELQEVIALTSELEESREKVLELEDELQESRGFRKKIKRLEES  
NKKLALALEHEKGKLTGLGQSNAALREHNSILETALAKREADLVQLNLQVQAVLQRKEE  
EDRQMKHLVQALQASLEKEKEKVNSLKEQVAAAKVEAGHNRRHFKAASLELSEVKEL  
QAKEHLVQKLQAEADDLQIREGKHSQEIAQFQAEAEARAQLQLLQKQLDEQLSKQPV  
GNQEMENLKWEVDQKEREIQSLKQQDLTEQQGRKELEGLQQLLQNVKSELEMAQED  
LSMTQKDKFMLQAKVSELKNNMKTLLQQNQQLKLDLRRGQDEKGAESAGQLFQPCA  
HQDPGLPSSRLAAGGAAETARREQGAPQEPEQLPPAAQAGDGQPAAPDGGARPDG  
ARVSVLVDAAGASHCQPCAPGGSRRPTRRPTETQSEQGFQRRAGRVTAVDSPPCAAA  
PEGSYQCYLFD CVVDVFLRHEI

SEQ ID No:110



MAPIGLKAVVGEKIMHDVIKKVKKKGWVVLVVDQLSMRMLSSCCKMTDIMTEGITIVED  
 INKRREPLPSLEAVYLITPSEKSVHSLISDFKDPPTAKYRAAHVFFTDSCPDALFNELVKS  
 RAAKVIKTLTEINIAFLPYESQVYSLDSADSFQSFYSPHKAQMKNPILERLAEQIATLCATL  
 KEYPAVRYRGEYKDNALLAQLIQDKLDAYKADDPTMGEGPDKARSQLLILDRGFDPSSP  
 VLHELTFQAMSYDLLPIENDVYKYETSGIGEARVKEVLLDEDDDLWIALRHKHIAEVSQE  
 VTRSLKDFSSSKRMNTGEKTTMRDLSQMLKKMPQYQKELSKYSTHLHLAEDCMKHYYQ  
 GTVDKLCRVEQDLAMGTDAEGEKIKDPMRAIVPILLDANVSTYDKIRIILLYIFLKNGITEE  
 NLNKLQHAQIPPEDSEITNMAHLGVPIVTDSTLRRRSKPERKERISEQTYQLSRWTPPIK  
 DIMEDTIEDKLDTKHYPYISTRSSASFSTTAVSARYGHWKKNKAPGEYRSGPRLIIFILGG  
 VSLNEMRCAYEVTQANGKWEVLIGSTHILTPTKFLMDLRHPDFRESSRVSFEDQAPTM  
 E

SEQ ID No:111

MATGGYRTSSGLGGSTTDFLEEWKAKREKMRAKQNPPGPAPPGGGSSDAAGKPPAG  
 ALGTPAAAAANELNNNLPGGAPAAPAVPGPGGVNCAVGSAMLTRAPPARGPRRSEDE  
 PPAASASAAPPQORDEEEDPGVPEKGKSSGPSARKGKGQIEKRKLREKRRSTGVVNIP  
 AAECLEDEYEDDEAGQKERKREDAITQQNTIQNEAVNLLDPGSSYLLQEPPRTVSGRYK  
 STTSVSEEDVSSRYSRTDRSGFPRYNRDANVSGTLVSSSTLEKKIEDLEKEVVTERQEN  
 LRLVRLMQDKEEMIGKLKEEIDLLNRDLDDIEDENEQLKQENKTLLKVVGQLTR

SEQ ID No:112

MKDRTQELRTAKDSDDDDDDVAVTVDRDRFMDEFFEQVEEIRGFIDKIAENVEEVKRKHS  
 AILASPNPDEKTKEELEELMSDIKKTANKVRSKLKSIEQSIEQEEGLNRSSADLRIRKTQH  
 STLSRKFEVVMSEYNATQSDYRERCKGRIQRQLEITGRITTTSEELEDMLESGNPAIFAS  
 GIIMDSSISKQALSEIETRHSEIIKLENSIRELHDMFMDMAMLVESQGEMIDRIEYNVEHAV  
 DYVERAVSDTKKAVKYQSKARRKKIMIIICCVILGIVIASTVGGIFA

SEQ ID No:113

MKDRTQELRSAKDSDDDEEEVVHVDRDHFMDEFFEQVEEIRGCIEKLSERVEDVQVKKQHS  
 AILAAPNPDEKTKQELEDLTADIKKTANKVRSKLKAIEQSIEQEEGLNRSSADLRIRKTQH  
 STLSRKFEVVMTEYNATQSKYRDRCKDRIQRQLEITGRITTTNEELEDMLESGKLAIFTDD  
 IKMDSQMTKQALNEIETRHNEIIKLETSIRELHDMFVDMAMLVESQGEMIDRIEYNVEHS  
 VDYVERAVSDTKKAVKYQSKARRKKIMIIICCVVLGVVLASSIGGTGL

SEQ ID No:114

MKDRLEQLKAKQLTQDDDDTAVEIAIDNTAFMDEFFSEIEETRLNIDKISEHVVEEAKKLYS  
IILSAPIPEPKTKDDLEQLTTEIKKRANNVRNKLKSMEKHIEEDEVRSSADLRIRKSQHSVL  
SRKFVEVMTKYNEAQVDFRERSKGRIQRQLEITGKKTTDEEELEEMLESGNPAIFTSGIID  
SQISKQALSEIEGRHKDIVRLESSIKELHDMFMDIAMLVENQGEMLDNIELNMHTVDHV  
EKARDESKKAVKYQSQARKKLIIVLVVVLLGILALIIGLSVGLN

SEQ ID No:115

MNHLEGSAEVEVTDEAAGGEVNESVEADLEHPEVEEEEQQQPPQQQHYVGRHQGRGA  
LEDLRAQLGQEEEEERGECLARSASTESGFHNHTDTAEGDVIAAARDGYDAERAQDPED  
ESAYAVQYRPEAEYETEQAEEAEHAEATHRRALPNHLHFHSLEHEEAMNAAYSGYVYTH  
RLFHRGEDEPYSEPYADYGGLQEHVYEEIGDAPELDARDGLRLYEQERDEAAAYRQEA  
LGARLHHYDERSDGEDSDPEKEAEFAPYPRMDSYEQEEDIDQIVAEVKQSMSSQSLDK  
AAEDMPEAEQDLERPPTPAGGRPDSPGLQAPAGQQRAVGPAGGGEAGQRYSEKRD  
AISLAIKDIKEAIEEVKTRTIRSPYTPDEPKEPIWVMRQDISPTRDCDDQRPMDGDSPSP  
GSSSPLGAESSSTSLHPSPDVEVPINKESRKSLASFPTYVEVPGPCDPEDLIDGIIFAANY  
LGSTQLLSDKTPSKNVRMMQAQEAVSRIKMAQKLAKSRKKAPEGESQPMTEVDLFILT  
QRIKVLNADTQETMMDHPLRTISYIADIGNIVVLMARRRIPRSNSQENVEASHPSQDGKR  
QYKMICHVFESEDAQLIAQSIGQAFSVAYQEFLRANGINPEDLSQKEYSDLLNTQDMYN  
DDLIHFSKSENCKDVFIKQKGEILGVVIVESGWGSILPTVIIANMMHGGPAEKSGKLNIG  
DQIMSINGTSLVGLPLSTCQSIKGLLENQSRVKLNIVRCPVTTVLIRRPDLRYQLGFSVQ  
NGIICSLMRGGIAERGGVRVGHRIIEINGQSVVATPHEKIVHILSNAVGEIHMKTMPAAMY  
RLLTAQEQPVYI

SEQ ID No:116

MALADSTRGLPNGGGGGGGSGSSSSSAEPPLFPDIVELNVGGQVYVTRRCTVVSVPD  
SLLWRMFTQQQPQELARDSKGRFFLDRDGFLFRYILDYLRDLQLVLPDYFPERSRLQR  
EAEIFELPELVRRLGAPQQPGPGPPPSRRGVHKEGSLGDELLPLGYSEPEQQEGASA  
GAPSPTELASRSPSGGAAGPLLTPSQSLDGSRRSYGITIGYRGSYTIGRDAQADAKFR  
RVARITVCGKTS LAKEVFGDTL NESRDPDRPPERYTSRYYLKFN FLEQAFDKLSESGFH  
MVACSSTGTCAFASSTDQSEDKIWTSYTEYVFCRE

SEQ ID No:117

MVMLLLLLLSALAGLFGAAEGQAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPTTFENG  
RCIQANYSLMENGKIKVLNQELRADGTVNQIEGEATPVNLTEPAKLEVKFSWFMPSPAY  
WILATDYENYALVYSCTCIIQLFHVDFAWILARNPNLPPETVDSLKNILTSNNIDVKKMTVT  
DQVNCPKLS

SEQ ID No:118

MLGGSGSHGRRSLAALSQIAYQRNDDDEEEAARERRRRRARQERLRQKQEEESLGQVT  
DQVEVNAQNSVPDEEAKTTTTNTQVEGDDEAAFLERLARREERRQKRLQEALERQKEF  
DPTITDASLSLPSRRMQNDTAENETTEKEEKSESQRERYEIEETETVTKSYQKNDWRDA  
EENKKEDKEKEEEEEEEKPKRGSIGENQGEEKGTKVQAKREKLQEDKPTFKKEEIKDEKI  
KKDKEPKKEEVKSFMDRKKGFTEVKSQNGEFMTHKLKHTENTFSRPGGRASVDTKEAE  
GAPQVEAGKRLEELRRRRRGETESEEFELKQKQQAALALEELKKKREERRKVLEEEE  
QRRKQEEADRKLREEEEEKRRLKEEIERRAEAAEKRQKMPEDGLSDDKKPFKCFTPKG  
SSLKIEERAFLNKSQKSSGVKSTHQAIVSKIDSRLEQYTS AIEGTKSAKPTKPAASDL  
PVPAEGVRNIKSMWEKGNVFSSPTAAGTPNKETAGLKVGVSRRINEWLTKTPDGNKSP  
APKPSDLRPGDVSSKRNLWEKQSVDKVTSPTKV

SEQ ID No:119

MLLSVPLLLGLLGLAVAEPVYFKEQFLDGDGWTSRWIESKHKSDFGKFVLSSGKFYG  
DEEKDKGLQTSQDARFYALSASFEPFSNKGQTLVVQFTVKHEQNIDCGGGYVKLFPNS  
LDQTDHMGDSEYNIMFGPDICGPGTKKVHVIFNYKGKNVLINKDIRCKDDEFTHLYTLIV  
RPDNTYEVKIDNSQVESGSLEDDWDFLPPKKIKDPDASKPEDWDERAKIDDPTDSKPE  
DWDKPEHIPDPDAKKPEDWDEEMDGEWEPPVIQNPEYKGEWKPRQIDNPDYKGTWIIH  
PEIDNPEYSPDPSIYAYDNFGVLGLDLWQVKSGTIFDNFLITNDEAYAEFNGNETWGVTK  
AAEKQMKDKQDEEQRLKEEEEDKKRKEEEEAEDKEDDEDKDEDEEDEEDKEEDEEED  
VPGQAKDEL

SEQ ID No:120

MLGLRPPLLALVGLLSLGCVLSECTKFKVSSCRECIESGPGCTWCQKLNFTGPGDPD  
SIRCDTRPQLLMRGCAADDIMDPTSLAETQEDHNGGQKQLSPQKVTLYLPGQAAAFN  
VTFRRAGYPIDLYYLMDSYSMLDDLNRNVKKLGGDLLRALNEITESGRIGFGSFVDKTV  
LPFVNTHPDKLRNPCPNKEKECQPPFAFRHVLKLTNNSNQFQTEVGKQLISGNLDAPE  
GGLDAMMQVAACPEEIGWRNVTRLLVFATDDGFHFAGDGKLGAILTPNDGRCHLEDNL  
YKRSNEFDYPSVGQLAHKLAENNIQPIFAVTSRMVKTYEKLTEIIPKSAVGELSESSNV

VHLIK NAYNKLSSRVFLDHNALPDTLKV TYDSFCSNGVTHRNQPRGDCDGVQINVPITF  
 QVKVTATECIEQEQSFVIRALGFTDIVTVQVLPQCECRCRDQSRDRSLCHGKGFLECGIC  
 RCDTGYIGKNCECQTQGRSSQELEGSCRKDNNSIICSGLGDCVCGQCLCHTSDVP GK  
 IYQQYCECDTINCERYNGQVCGGPGRGLCF CGKCRCHPGFEGSACQCERTTEGCLNP  
 RRVECSGRGRRCRCNVCECHSGYQLPLCQECPCGSPCGKYISCAECLKFEKGPF GK  
 CSAACPGLQLSNNPVKGR TCKERDSEGCWVAYTLEQQDGM DRYLIYVDESRECVAGP  
 NIAAIVGGTVAGIVLIGILLLV IWKALIHLSDLREYRRFEKEKLSQWNNDNPLFKSATTTV  
 MNP KFAES

SEQ ID No:121

MWRLRRAAVACEVCQSLVKHSSGIKGS LPLQKLHLVSR SIYHSHHPTLKLQRPQLRTSF  
 QQFSSLTNLPLRKLKFSPIKYGYQPRRNFWPARLATRLLKRLYLILGSAVGGGYTAKKTF  
 DQWKDMIPDLSEYKWIVPDIVWEIDEYIDFGSPEETA FRATDRGSESDKHFRKGLLGELI  
 LLQQQIQEHEEEARRAAGQYSTSYAQQKRKVSDKEKIDQLQEELLHTQLKYQRILERLE  
 KENKELRKLVLQKDDKGIHHRKLKSLIDMYSEVLDVLS DYDASYNTQDHLPRVVVVG D  
 QSAGKTSVLEMIAQARIFPRGSGEMMTRSPVKVTLSE GPHHVALFKDSSREFDLTKEED  
 LAALRHEIELMRKNVKEGCTVSPETISLNVKG PGLQRMVLVDLPGVINTVTSGMAPDT  
 KETIFSISKAYMQNPNAIILCIQDGSVDAERSIVTDLVSQMDPHGRR TIFVLTKVDLAEKN  
 VASPSRIQQIIEGKLFP MKALGYFAVVTGKGNSSESIEAIREYEEEEFFQNSKLLKTSMLKA  
 HQVTTRNL SLAVSDCFWKMVRESVEQQADSFKATRFNLET EWKNNYPRLRELD RNEL  
 FEKAKNEILDEVISLSQVTPKHWE EILQQSLWERVSTHVIENIYLPAAQTMNSGTFNTTV  
 DIKLKQWTDKQLPNKAVEVAWETLQEEFSRFMTE PKGKEHDDIFDKLKEAVKEESIKRH  
 KWNDFAEDSLRVIQHNALEDRSISDKQQWDAAIYFMEEALQARLKDTENAIENMVGPD  
 WKKRWLYWKNRTQEQC VHNETKNELEKMLKCNEEHPAYLASDEITTVRKNLESRGVE  
 VDPSLIKDTWHQVYRRHFLKTALNHCNLCRRGFYYYQRHFVDSELECNDVVLFWRIQR  
 MLAITANTLRQQLTNT EVRRLEKNVKEVLEDFAEDGEKKIKLLTGKRVQLAEDLKKVREI  
 QEKLD AFIEALHQEK

SEQ ID No:122

MLSQVYRCGFQPFNQHLLPWVKCTTVFRSHCIQPSVIRHVRSWSNIPFITVPLSRTHGK  
 SFAHRSELKHAKRIVVKLGS AVVTRGDECGLALGRLASIVEQVSVLQNNQGREMMLVTS  
 GAVAFGKQRLRHEILLSQSVRQALHSGQNQLKEMAIPVLEARACAAAGQSGLMALYEA  
 MFTQYSICAAQILVTNLD FHDEQKRRNLNGTLHELLRMNIVPIVNTNDAVVPPAEPNSDL  
 QGVNVISVKDNDSLAA RLAVEMKTDLLIVLSDVEGLFDSPPGSDDAKLIDIFYPGDQQSV

TFGTKSRVGMGGMEAKVKAALWALQGGTSVVIANGTHPKVSGHVITDIVEGKKVGTFF  
 SEVKPAGPTVEQQGEMARSGGRMLATLEPEQRAEIIHHLADLLTDQRDEILLANKKDLE  
 EAEGRLAAPLLKRLSLSTSKLNSLAIGLRQIAASSQDSVGRVLRRTRIAKNLELEQVTVPI  
 GVLLVIFESRPDCLPQVAALAIASGNGLLLKGGKEAAHSNRILHLLTQEALSIHGVKEAVQ  
 LVNTREEVEDLCRLDKMIDLIIPRGSSQLVRDIQKAAKGIPVMGHSEGICHMYVDSEASV  
 DKVTRLVRDSKCEYPAACNALETLLIHRDLLRTPLFDQIIDMLRVEQVKIHAGPKFASYLT  
 FSPSEVKSLRTEYGDLELCIEVVDNVQDAIDHIHKYGSSTHDVIVTEDENTAEEFFLQHVD  
 SACVFWNASTRFSDGYRFGGLGAEVGISTSRIHARGPVGLEGLLTTKWLLRGKDHVVSD  
 FSEHGSLKYLHENLPIQRNTN

SEQ ID No:123

MTELPAPLSYFQNAQMSEDNHLSTNDNRERQEHNDRSLGHPEPLSNGRPQGNSR  
 QVVEQDEEEDEELTKYGAKHVIMLFVPVTLCMVVVVATIKSVSFYTRKDGQLIYTPFTE  
 DTETVGQRALHSILNAAIMISVIVVMTILLVVLYKYRCYKVIHAWLISSLLLLFFFSFIYLGE  
 VFKTYNVAVDYITVALLIWNLGVVGMISIHWKGPLRLQQAYLIMISALMALVFIKYLPEWT  
 AWLILAVISVYDLVAVLCPKGPLRMLVETAQERNETLFPALIYSSTMVWLVNMAEGDPEA  
 QRRVSKNSKYNAESTERESQDTVAENDDGGFSEWEAQRDShLGPHRSTPESRAAV  
 QELSSSILAGEDPEERGVLGLGDFIFYSVLVGKASATASGDWNTTIACFVAILIGLCLTL  
 LLLAIFKKALPALPISITFGLVFYFATDYLVPFMDQLAFHQFYI

SEQ ID No:124

MSTGGDFGNPLRKFKLVFLGEQSVGKTSLITRFMYDSFDNTYQATIGIDFLSKTMYLED  
 RTVRLQLWDTAGQERFRSLIPSYIRDSTVAVVVYDITNVNSFQQTTKWIDDVTERGSD  
 VIIMLVGNKTDLADKRQVSIEEGERKAKELNVMFIETSAKAGYNVKQLFRRVAAALPGME  
 STQDRSREDMIDIKLEKPQEQPVSEGGCSC

SEQ ID No:125

MADNLSDTLKKLKITAVIDKTEDSLEGCLDCLLQALAQNNNTETSEKIQASGILQLFATLLTP  
 QSSCKAKVANIIAEVAKNEFMRIPCVDAGLISPLVQLLSKDKQEVLLQTGRALGNICYDS  
 HEGRSADVQAGGAQIVIDHLRSLCSITDPANEKLLTVFCGMLMNYSNENDSLQAQLINM  
 GVIPTLVKLLGIHCQNAALTEMCLVAFGNLAELESSKEQFASTNIAEELVKLFKKQIEHDK  
 REMIFEVLAPLAENDAIKLQLVEAGLVECLLEIVQQKVDSKEDDITELKTGSDLMVLLLL  
 GDESMQKLFEGGKGVSFQRVLSWIPSNHQLQLAGALAIANFARNDANCIHMVDNGIV  
 EKLMDLLDRHVEDGNVTVQHAALSALRNLAIPVINKAKMLSAGVTEAVLKFLKSEMPPV

QFKLLGTLRMLIDAQEAQQLGKNVKLVERLVEWCEAKDHAGVMGESNRLLSALIRHRSK  
SKDVIKTIVQSGGIKHLVTMATSEHVIMQNEALVALALIAALELGTAEKDLES AKLVQILHR  
LLADERSAPEIKYNSMVLICALMGSECLHKEVQDLAFLDVVSKLRSHENKSVAQQASLT  
EQRLTVES

SEQ ID No:126

MPGPSPGLRRALLGLWAALGLGLFGLSAVSQEPFWADLQPRVAFVERGGSLWLNCS  
NCPRPERGGLETSLRRNGTQRGLRWLARQLVDIREPETQPVCFRCARRTLQARGLIR  
TFQRPDRVELMPLPPWQPVGENFTLSCRVPGAGPRASLTLLRGAQELIRRSFAGEP  
PRARGAVLTATVLRREDHGANFSCRAELDLRPHGLGLFENS SAPRELRTFSLSPDAP  
RLAAPRLLEVGSERPVSCTLDGLFPASEARVYLALGDQNLSPDVTLEGDAFVATATATA  
SAEQEGARQLVCNVTLGGENRETR ENVTIYSFPAPLLTLSEPSVSEGQMTVTCAAGA  
QALVTLEGVPAAVPGQPAQLQLNATENDDRRSFFCDATLDVDGETLIKNRSAELRVLYA  
PRLDDSDCPRS WTWPEGPEQTLRCEARGNPEPSVHCARS DGGAVLALGLLGPVTRAL  
SGTYRCKAANDQGEAVKDVTLTVEYAPALDSVGCPERITWLEGTEASLSCVAHGVP  
DVICVRSGELGAVIEGLLRVAREHAGTYRCEATNPRGSAAKNVAVTVEYGPRFEESP  
SNWTWVEGSGRLFSCEVDGKPQPSVKCVGSGGTTEGVLLPLAPPDPSPRAPRIPRVL  
APGIYVCNATNRHGSVAKTVVVS AESPPPEMDESTCPSHQTWLEGAEASALACAARGR  
PSPGVRCSREGIPWPEQQRVSREDAGTYHCVATNAHGTDSRTVTVGVEYRPVVAELA  
ASPPGGVRPGGNFTLT CRAEAWPPAQISWRAPRALNIGLSSNNSTLSVAGAMGSHG  
GEYECARTNAHGRHARRITVRVAGPWLWVAVGGAAGGAALLAAGAGLAFYVQSTACK  
KGEYNVQEAESSGEAVCLNGAGGGAGGAAGAEGGPEAAGGAAESPAEGEVFAIQLTS

A

SEQ ID No:127

MAAGPSGCLVPAFGLRLLLATVLQAVSAFGAEFSSEACRELGFSSNLLCSCDLLGQFN  
LLQLDPDCRGCCQEEAQFETKKLYAGAILEVCGCKLGRFPQVQAFVRS DKPKLFRGLQI  
KYVRGSDPVLKLLDDNGNIAEELSILKWNTDSVEEFLSEKLERI

SEQ ID No:128

MDAEFRHDSGYEVHHQKL VFFAEDVGSNKGAIIGLMVGGVVIATVIVITLVMLKKKQYTSI  
HHGVVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID No:129

MAQALPWLLLWMGAGVLP AHGTQH GIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRR  
 GSFVEMVDNLRGKSGQGYVEMTVGSPQTLNILVDTGSSNFAVGAAPHPFLHRYYQ  
 RQLSSTYRDLRKGVVVPYTQGWEGELGTDLVSIHPGNVTVRANIAAITESDKFFINGS  
 NWEGLGLAYAEIARPDSDLFFDSL VKQTHVPNLFSLQLCGAGFPLNQSEVLASVGG  
 SMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTN  
 LRLPKKVFEAAVKSIIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVT  
 NQSFRITILPQQYL RPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRI  
 GFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDESTLMTIAYVMAAICALFMLP  
 LCLMVCQWRCLRCLRQQHDDFADDISLLK

SEQ ID No:130

MPKGRQKVPHLDAPLGLPTCLWLELAGLFLLPWVMGLAGTGGPDGQGTGGASWAV  
 HLESLEGDGEEETLEQQADALAQAAGLVNAGRIGELQGHYLFVQPAHRPALEVEPIR  
 QQVEAVLAGHEAVRWHSEQRLLRRAKRSVHFNDPKYPQQWHLNNRRSPGRDINVTG  
 VWERNVTGRGVTVVVDDGVEHTIQDIAPNYSPEGSYDLNSNDPDPMPHPDVENG NH  
 HGTRCAGEIAAVPNNSFCAVGVAYGSRIAGIRVLDGPLTDSMEAVAFNKHYQINDIYSCS  
 WGPDDD GKTVDGPHQLGKAALQHGVIAGRQGFGSIFVVASGNGGQHNDNCNYDGYA  
 NSIYTVTIGAVDEEGRMPFYAEECASMLAVTFSGGDKMLRSIVTTDWDLQKGTGCTEG  
 HTGTSAAAPLAAGMIALMLQVRPCLTWRDVQHIIVFTATRYEDRRAEWVTNEAGFSHS  
 HQHGFGLLNAWRLVNAAKIWTSVPYLASYVSPVLKENKAIPQSPRSLEVLWNVSRMDL  
 EMSGLKTLEHVAVTVSITHPRRGSLELKLFCPSGMMSLIGAPRSMDSDPNGFNDWTF S  
 TVRCWGERARGTYRLVIRDVGDES FQVGILRQWQLTLYGSVWSAVDIRDRQRLL ESAM  
 SGKYLHDDFALPCPPGLKIPEEDGYTITPNTLKTLLVVGCFVFWTVYYMLEVYLSQRNV  
 ASNQVCRSGPCHWPHRSRKAKEEGTELESVPLCSSKDPDEVETESRGPPTTSDLLAP  
 DLLEQGDWSLSQNKSAIDCPHQHLDVPHGKEEQIC

SEQ ID No:131

GGGSCRGRGLQRASGLRARRGLERQTAQWAEKEAQPPWPVMEMEKEFEQIDKSG  
 SWAAIYQDIRHEASDFPCRVAKL PKNKNRNRVYRDVSPFDHSRIKLHQEDNDYINASLIK  
 MEEAQRSYILTQGPLPNTCGHFWEMVWEQKSRGVVMLNRVMEKGS LKCAQYWPQKE  
 EKEMIFEDTNLKLTLISEDIKSYTVRQLELENLTTQETREILHFHYTTWPDFGVPESPAS  
 FLNFLFKVRESGSLSPEHGPVVVHCSAGIGRSGTFCLADTCLLLMDKRKDPSSVDIKKV  
 LLEM RKFRMGLIQTADQLRFSYLAVIEGAKFIMGDSSVQDQWKELSHEDLEPPPEHIPP  
 PPRPPKRILEPHNGKCREFFPNHQWVKEETQEDKDCPIKEEKG SPLNAAPYGIESMSQ

DTEVRSRVVGGSLRGAQAASPAKGEP SLPEKDEDHALSYWKPFLVNM CVATVLTAGA  
YLCYRFLFNSNT

SEQ ID No:132

MEARVERAVQKRQVLFLCVFLGMSWAGAEPLRYFVAEETERGTFLT NLAKDLGLGVGE  
LRARGTRIVSDQNMQILLSSLTG DLLLNEKLDREELCGPREPCVLPFQ LLLLEKPFQIFRA  
ELWVRDINDHAPVFLDREISLKILESTTPGA AFLLESAQDSDVGTNSLSNYTISP NAYFHI  
NVHDSGEGNIYPELV LNQVLDREEIPEFSLT LTALDGGSPPRSGTALVRILVLDVNDNAP  
DFVRSLYKVQVPENSPV GSMVVSVSARDLDTGSNGEIAYAFSYATERILKTFQINPTSG  
SLHLKAQLDYEA IQTYTLTIQAKDGGGLSGKCTVVVDVTDINDNRPELLSSLTSP IAENS  
PETVVAVFRIRDRDSGNNGKTVCSIQDDVPFILKPSVENFYTLVTEKPLDRERNTEYNITI  
TVTDLGTPRLKTEHNITVLVSDVNDNAPAFTQT SYTLFVRENNSPALPIG SVSATDRDSG  
TNAQVIYSLLPSQD PHLPLASLV SINADNGHLFALRSLDY EALQAFEF RVGATDRGSPAL  
SSEALVRVLVLDANDNSPFVLYPLQNSSAPCTEPLPRAAEPGYLVTKVVAVDGD SGQN  
AWLSYQLLKATEPGLFGVWAHNGEVRTARLLSERDAAKQRLVVLVKDNGEP PRSATAT  
LHVLLVDGFSQPYLRLPEAAPDQANSLTVYLVALASVSSLFLLSVLLFVAVRLCRRSRA  
APVGRC SVPEGPFPRHLVDLSGTGTLSQSYQYEVCLTGGSGTNEFKFLKPIIPNLL PQS  
TGREVEENRPFQNNLGF

SEQ ID No:133

MDPLFQQTHKQVHEIQSCMGRLETADKQSVHIVENEIQASIDQIFSR LERLEILSSKEPP  
NKRQNARLRVDQLKYDVQHLQTALRN FQHRRHAREQQERQREELLSRTFTTNDSDTTI  
PMDES LQFNSSLQKVHNGMDDLILDGHNILDGLRTQRLTLKGTQKKILD IANMLGLSNTV  
MRLIEKRAFQDKYFMIGGMLLTCVVMFLVVQYLT

SEQ ID No:134

MDNSGKEAEAMALLAEAERKVKNSQSFFSGLFGGSSKIEEACEIYARAANMF KMAKNW  
SAAGNAFCQAAQLHLQLQSKHDAATCFVDAGNAFKKADPQEAINCLMRAIEIY TDMGRF  
TIAAKHHISIAE IYETELVDIEKAI AHYEQSADYYKGEESSANKCLLKVAGYAALLEQYQ  
KAIDIYEQVG TNAMDTPLLKYSADYFFKAALCHFCIDMLNAKLAVQKYEELFPAFSDSR  
ECKLMKKLLEAH EEQNVDSYTESVKEYDSISR LDQWLTTMLLRIKKT IQGDEEDLR

SEQ ID No:135



MSVPSSLSQSAINANSHGGPALSPLPLHAAHNQLLNAKLQATAVGPKDLRSAMGEGG  
GPEPGPANAKWLKEGQNQLRRAATAHRDQNRNVTLTAAEEASQEPEMAPLGPKGLIHL  
YSELELSAHNAANRGLRGPGLIISTQEQQPDEGEKEKAAGEAEEEEEDDDDEEEEEEDLS  
SPPGLPEPLESVEAPPRPQALTDGPREHSKSASLLFGMRNSAASDEDSSWATLSQGSP  
SYGSPEDTDSFWNPNAFETDSDLPAWGMVRVQDTSQTYYYWHIPTGTTQWEPPGRASP  
SQGSSPQEESQLTWTGFAHGEGFEDGEFWKDEPSDEAPMELGLKEPEEGTLTFPAQS  
LSPEPLPQEEELPPRNTNPGIKCFAVRSLGWVEMTEEELAPGRSSVAVNNCIRQLSYH  
KNNLHDPMSGGWGEGKDLLLQLEDETLKLVEPQSQALLHAQPIISIRVWGVGRDSGRE  
RDFAYVARDKLTQMLKCHVFRCEAPAKNIATSLHEICKIMAERRNARCLVNGLSLDHS  
KLVDVPFQVEFPAPKNELVQKFQVYYLGNVPVAKPVGVDVINGALESVLSSSSSREQWT  
PSHVSVAPATLTILHQQTEAVLGEQVRFLSFLAVGRDVHTFAFIMAAGPASFCCHMFW  
CEPNAASLSEAVQAACMLRYQKCLDARSQASTSCLPAPPAESVARRVGWTVRRGVQS  
LWGSCLKPKRLGAHTP

SEQ ID No:136

MAAPQDVHVRICNQEIVKFDLEVKALIQDIRDCSGPLSALTELNTKVKEKFQQLRHRIQD  
LEQLAKEQDKESKQLLLQEVENHKKQMLSNQASWRKANLTCKIAIDNLEKAELLQGGD  
LLRQRKTTKESLAQTSSTITESLMGISRMMAQQVQQSEAMQSLVTSSRTILDANEEFK  
SMSGTIQLGRKLITKYNRRELTDKLLIFLALRLFLATVLYIVKKRLFPFL

SEQ ID No:137

MRRAGLGEGVPPGNYGNYGYANSYGYSACEEENERLTESLRSKVTAIKSLSIEIGHEVKT  
QNKLLAEMDSQFDSTTGFLGKTMGKLKILSRGSQTKLLCYMMLFSLFVFFIYWIILR

SEQ ID No:138

MFLVNSFLKGGGGGGGGGGGGGLGGGLGNVLGGLISGAGGGGGGGGGGGGGGGGGGGG  
GGTAMRILGGVISASEAAQYNPEPPPPRTHYSNIEANESEEVRRQFRRLFAQLAGDDM  
EVSATELMNINLVVTRHPDLKTDGFGIDTCRSMVAVMDSDTTGKLGFEFEFKYLWNNIK  
RWQAIYKQFDTDRSGTICSSSELPGAFAEAGFHLNEHLYNMIIRRYSDSGNMDFDNFIS  
CLVRLDAMFRAFKSLDKDGTGQIQVNIQEWLQLTMYS

SEQ ID No:139

MASFVTEVLAHSGRLEKEDLGTRISRLTRRVEEIKGEVCNMISKKYSEFLPSMQSAQGLI  
TQVDKLSIEDIDLLKSRIESEVRRDLHVSTGEFTDLKQQLERDSVVLSSLLKQLQEFSTAIEE

YNCALTEKKYVTGAQRLEEAQKCLKLLKSRKCFDLKILKSLSMELTIQKQNILYHLGEEW  
 QKLIVWKFPSPSKDTSSLESYLQTELHLYTEQSHKEEKTMPMPISSVLLAFSVLGELHSLK  
 KSFGQMLLKYILRPLASCPSLHAVIESQPNIVIIRFESIMTNLEYPPSPSEVFTKIRLVLEVLO  
 KQLLDLPLDLDLENEKTSTVPLAEMLGDMIWEDLSECLIKNCLVYSIPTNSSKLQQYEEII  
 QSTEEFENALKEMRFLKGDTTDLLKYARNINSHFANKKCCQDVIVAARNLMTSEIHNTVKII  
 PDSKINVPELPTPDEDNKLEVQKVSNTQYHEVMNLEPENTLDQHSFSLPTCRISESVKK  
 LMELAYQTLLEATTSSDQCAVQLFYSVRNIFHLFHDVVPTYHKENLQKLPQLAAIHHNNC  
 MYIAHHLLTLGHQFRLRLAPILCDGTATFVDLVPGFRRLGTECFLAQMRAQKGELLERLS  
 SARNFSNMDDEENYSAASKAVRQVLHQLKRLGIVWQDVLVNIYCKAMGTLLNTAISEV  
 IGKITALEDISTEDGDRLYSLCKTVMDEGPQVFAPLSEESKNKKYQEEVPVYVPKWMPF  
 KELMMMLQASLQEIGDRWADGKGPLAAAFSSSEVKALIRALFQNTERRAAALAKIK

SEQ ID No:140

MADPKYADLPGIARNEPDVYETSDLPEDDQAEFDAAELTSTSVEHIIVNPNAAYDKFKDK  
 RVGTKGLDFSDRIGKTKRTGYESGEYEMLGEGLGVKETPQQKYQROLLHEVQELTTEVE  
 KIKTTVKESATEEKLTPVLLAKQLAALKQQLVASHLEKLLGPDAAINLTDPDGALAKRLLL  
 QLEATKNSKGGSGGKTTGTPPDSSLVTYELHSRPEQDKFSQAAKVAELEKRLTELETA  
 VRCDQDAQNPLSAGLQGACLMETVELLQAKVSALDLAVLDQVEARLQSVLGKVNEIAK  
 HKASVEDADTQSKVHQLYETIQRWSPIASTLPVLVQRLVTIKQLHEQAMQFGQLLTHLD  
 TTQQMIANSLKDNTLLTQVQTTMRENLATVEGNFASIDERMKKLGK

SEQ ID No:141

MRTLILLVLWLATRGSALYFHIGETEKKCFIEEIPDETMVIGNYRTQLYDKQREEYQPATP  
 GFGMCVEVKDPEDKVILAREYGSEGRFTFTSHTPGEHQICLHSNSTKFSLFAGGMLRV  
 HLDIQVGEHANDYAEIPAKDKLSELQLRVRQLVEQVEQIQKEQNYQRWREERFRQTSE  
 STNQRVLWWSILQTLILVAIGVWQMRHLKSFFEAKKL

SEQ ID No:142

MASSGAGDPLDSKRGEAPFAQRIDPTREKLTPEQLHSMRQAELAQWQKVLPRRRTRNI  
 VTGLGIGALVLAIYGYTFYSISQERFLDELEDEAKAARARALARASGS

SEQ ID No:143

KAPGSETKATRPGAWPTPGTSTPRPRKWLSARARVSRSIQLSTGRRRTLLLTSAETA  
 RTSLGTRRRRRAPRFCPTSAWGSGPARMRAARRGLHCAGAERPRRRGRLWDSSGVP

QRQKRPGPWRTQTQEQMSRDVCIHTWPCTYYLEPKRRWVTGQLSLTSLSLRFMTDST  
GEILVSFPLSSIVEIKKEASHFIFSSITILEKGHAKHWFSSLRPSRNVVFSIIEHFWRELLLS  
QPGAVADASVPRTTRGEELTGLMAGSQKRLEDTARVLHHQGGQQLDSVMRGLDKMESD  
LEVADRLLTELESPAWWPFSSKLWKTPPETKPREDSMTSCEPFGKEGILIKIPAVISHR  
TESHVKPGRLTVLVSGLEIHDSSSLLMHRFEREDVDDIKVHSPYEISIRQRFIGKPD MAY  
RLISAKMPEVIPILEVQFSKKMELLEDALVLR SARTSSPAEKSCSVWHAASGLMGCTLHR  
EPPAGDQEGTALHLQTSLPALSEADTQELTQILRRMKGLALEAESELERQDEALDGVA A  
AVDRATLTIDKHNRRMKRLT

SEQ ID No:144

SKSPGAQFPEAVSSERSSCTVVSQVCESPTMSASGVLSFTQQGWEQVLAKVKRAVVY  
LDAACAESLHWGCGSTRLLEAVGGPDCHLREFEPDAIGGGAKQPKAVFVLSCLLKGR T  
VEILRDIICRSHFQYCVVVTTVSHAVHLTANHVPAAAAAEMEGQQPVFEQLEEKLC EWM  
GNMNYTAEVFHVPLLLAPVAPHFALT PAFASLFP LLPQDVHLLNSARPDKRKLGS LGDV  
DSTTLTPELLLQIRCLVSGLSSLCEHLGVREECF AVGSLSQVIAADLANYAPAKNRK KTA  
AGRASVVFDRTLDLTGAVGHHGDNLVEKIISALPQLPGHTNDVMVMNMIALTALHTE EE  
NYNVVAPGCLSQSSDTTAKALWEALLNTKHKEAVMEVRRHLVEAASRENLP IKMSMGR  
VTPGQLMSYIQLFKNNLKALMNHCGLLQLGLATAQTLKHPQTAKWDNFLAFERLLLQ SI  
GESAMSVVLNQLLPMIKPVTQRTNEDYSPEELLILLIYISVTGELTVDKDLCEAE EKVKK  
ALAQVFCEESGLSPLLQKITDWDSSINLTFHKSKI AVDELFTSLRDIAGARSLLKQF KSVY  
VPGNHHTHQASYKPLLKQVVVEIFHPERPDSVDIEHMSSGLTDLLKTGF SMFMKVS RPHP  
SDYPLLILFVVGGVTVSEVKMVKDLVASLKPGTQVIVLSTRLLKPLNIPELLFATDRLHP D  
LGF

SEQ ID No:145

MAASRLELNLRLLSRCEAMAAEK RDPDEWRLEKYVGALEDMLQALKVHASKPASEVI  
NEYSWKVDFLKGMLQAEKLTSSSEKALANQFLAPGRVPTTARERVPATKTVHLQSRAR  
YTSEMRSELLGTDSAEPMDVRKRTGVAGSQPVSEKQSAAELDLVLQRHQNLQE KLA  
EEMLG LARSLKTNTLAAQSVIKDNQTLSHSLKMADQNLEKLKTESERLEQHTQKSVN  
WLLWAMLIIVCFIFISMILFIRIMPKLK

SEQ ID No:146

MVDQLEQILSVSELLEKHGLEKPISFVKNTQSSSEEARKLMVRLTRHTGRKQPPVSESH  
WRTLLQDMLTMQQNVYTCLDSDACYEIFTESLLCSSRLENIHLAGQMMHCSACSENPP

AGIAHKGKPHYRVSYEKSIDLVLAAASREYFNSSTNLTDSMDLARCCQLITDRPPAIQE  
ELDLIQAVGCLEEFVGEILPLQVRLCPDRISLIKECISQSPTCYKQSTKLLGLAELLRVAGE  
NPEERRGQVLILLVEQALRFHDYKAASMHCQELMATGYPKSWDVCSQLGQSEGYQDL  
ATRQELMAFALTHCPPSSIEMLLAASSSLQTEILYQRVNFQIHHEGGENISASPLTSKAVQ  
EDEVGVPGSNSADLLRWTTATTMKVLSNTTTTTTKAVLQAVSDGQWWKSLTYLRPLQ  
GQKCGGAYQIGTTANEDLEKQGCHPFYESVISNPFVAESEGYDTYQHVPVESFAEVLL  
RTGKLAEAKNKGEVFPTEVLLQLASEALPNDMTLALAYLLALPQVLDANRCFEKQSPS  
ALSLQLAAYYYSLQIYARLAPCFRDKCHPLYRADPKELIKMVTRHVTRHEHEAWPEDLIS  
LTKQLHCYNERLLDFTQAQILQGLRKGVDVQRFTADDQYKRETI GLAETLEESVYSIAIS  
LAQRYSVSRWEVFMTHLEFLFTDSGLSTLEIENRAQDLHLFETLKTDPFAHQHVMKYI  
YPTIGGFDHERLQYYFTLLENCGCADLGNCAIKPETHIRLLKKFKVVASGLNYKKLTDEN  
MSPLEALEPVLSSQNILSISKLVPKIPEKDGQMLSPSSLYTIWLQKLFWTGDPHLIKQVPG  
SSPEWLHAYDVCMKYFDRLHPGDLITVVDVAVTFSPKAVTKLSVEARKEMTRKAIKTVKH  
FIEKPRKRNSEDEAQEAKDSKVTYADTLNHLEKSLAHLETLSHSFILSLKNSEQETLQKY  
SHLYDLRSRSDKEKLHDEAVAICLDGQPLAMIQQLLEVAVGLLNISTKDIVQSAIMKIISALS  
GGSADLGGPRDPLKVLEGVVAHAVHASVDKGEELVSPEDLLEWL RPF CADD AWPVRPRI  
HVLQILGQS FHLTEEDSKLLVFFRTEAILKASWPQRQVDIADIENEENRYCLFMELLESS  
HHETEFQHLVLLLQAWPPMKSEYVITNNPWVRLATVMLTRCTMENKEGLGNEVLKMC R  
SLYNTKQMLPAEGVKELCLLLLNQSLLLPSLKLLLES RDEHLHEMALEQITAVTTVND SN  
CDQELSLLLDAKLLVKCVSTPFYPRIVDHLLASLQQGRWDAEELGRHLREAGHEAEAG  
SLLAVRGTHQAFRTFSTALRAAQHWVLKPPVALLLSRKSIWS

SEQ ID No:147

RRMNHKSKKRIREAKRSARPELKDSL DWTRHNYYESFSLSPA AVADNVERADALQLSV  
EEFVERYERPYKPVLLNAQEGWSAQEKWTLERLKRKYRNQKFKCGEDNDGYSVKMK  
MKYYIEYMESTRDDSPYIFDSSYGEHPKRRKLEDYKVPKFFTD DLFQYAGEKRRPPY  
RWFVMGPPRSGTGIHIDPLGTS AWNALVQGHKRWCLFPTSTPRELIKVTRDEGGNQQ  
DEAITWFNVIYPRTQLPTWPPEFKPLEILQKPGETVFVPGGWWHVVLNLDTTIAITQNFA  
SSTNFPVWWHKTVRGRPKLSRKWYRILKQEHPELAVLADSVDLQESTGIASDSSSDSSS  
SSSSSSSDSDSECESGSEGDGTVHRRKKRRTCSMVGN GDTTSQDDCVSKERSSSRIR  
DTCGGRAHP

SEQ ID No:148

MGSECVAGLSQTPQATLAANGAEDSRGGEMPLPAGEIGASPAAPCCSESGDERKNLEE  
 KSDINVTVLIGSKQVSEGTDNGDLPYSYVSFAFIEKEVGNDLKSLKKLDKLEQRTVSKMQL  
 EEQVLTISSEIPKRIRSALKNAEESKQFLNQFLEQETHLFSAINSHLLTAQPWMDDLGTMI  
 SQIEEIERHLAYLKWISQIEELSDNIQQYLMTNNVPEAASTLVSMAELDIKLQESSCTHLL  
 GFMRA TVKFWHKILKDKLTSDFEELAQLHWPFIAPPQSQT VGLSRPASAPEIYSYLETL  
 FCQLLKLQTSDELLTEPKQLPEKYSLPASPSVILPIQVMLTPLQKRFRYHFRGNRQTNVL  
 SKPEWYLAQVLMWIGNHTEFLDEKIQPILDKVGSVLNARLEFSRGLMMLVLEKLATDIPC  
 LLYDDNLFCHLVDEVLLFERELHSVHGYPGTFASCMHILSEETCFQRWLTVERKFALQK  
 MDSMLSSEA AWVSQYKDITD VDEM KVPDCAET FMTLLL VITDRYKNLPTASRKLFLEL  
 QKDLVDDFRIRLTQVMKEETRASLGFRYCAILNAVNYISTVLADWADNVFFLQLQQAAL  
 VFAENNTLSKLQLGQLASMESSVFDDMINLLERLKHDMLTRQVDHVFREVKDAAKLYKK  
 ERWLSLPSQSEQAVMSLSSSACPLLLTLRDHLLQLEQQLCFSLFKIFWQMLVEKLDVYIY  
 QEILANHFNEGGAQLQFDMTRNLFP LFSHYCKRPENYFKHIKEACIVLNLNVGSALLK  
 DVLQSASGQLSTTAALNEVGIYKLAQQDVEILLNLRTNWPNTGK

SEQ ID No:149

MVLLTMIARVADGLPLAASMQEDEQSGRDLQQYQSQAQQLFRKLNEQSPTRCTLEAGA  
 MTFHYIIEQGVCYLVLC EAAPK KLAFAYLEDLHSEFDEQH GKKVPTVSRPYSFIEFDTFI  
 QKTKKLYIDSRARRNLGSINTELQDVQRIMVANIEEVLQRGEALSALDSKANNLSSLSKK  
 YRQDAKYLNMRSTYAKLA AVAVFFIMLIVYVRFWWL

SEQ ID No:150

MSLED PFFVVRGEVQKAVNTARGLYQRWCELLQESA AVGREELDWT TNELRNLRSIE  
 WDLEDLEETIGIVEANPGKFKLPAGDLQERKVFVERMREAVQEMKDHMVSP TAVAFLE  
 RNNREILAGKPAAQKSPSDLLDASAVSATSRYIEEQQATQQLIMDEQDQQLEMVSGSIQ  
 VLKHMSGRVGEELDEQGIMLDAFAQEMDHTQSRMDGVLRKLAKVSHMTSDRRQWCAI  
 AVLVGVL LLLVLILLFSL

SEQ ID No:151

MAVDITLLFRASVKTVKTRNKALGVAVGGGV DGSRDELFR RSPRPKGDFSSRAREVISH  
 IGKLRDFLLEHRKDYINAYSHTMSEYGRMTDTERDQIDQDAQIFMRTCSEAIQQLRTEA  
 HKEIHSQQVKEHRTAVLDFIEDYLKRVCKLYSEQRAIRVKRVVDKKRLSKLEPEPNTKTR  
 ESTSSEKVSQSPSKDSEENPATEERPEKILAETQPELGTWGDGKGEDELSPEEIQMFE

QENQRLIGEMNSLFDEVQRQIEGRVVEISRLQEIFTEKVLQQEAEIDSIHQLVVGATENIKE  
GNEDIREAIKNNAGFRVWILFFLVMCSFSLLFLDWYDS

SEQ ID No:152

MSCRDRTQEFLSACKSLQTRQNGIQTNKPALRAVRQRSEFTLMAKRIGKDLSENTFAKLE  
KLILAKRKSLFDDKAVEIEELTYIHKQDINSLNKQIAQLQDFVRAKGSQSGRHLQTHSNTI  
VVSLLQSKLASMSNDFKSVLEVRTENLKQQRSRREQFSRAPVSALPLAPNHLGGGAVVL  
GAESHASKDVAIDMMDSRTSQQLQLIDEQDSYIQSRADTMQNIESTIVELGSIFQQLAHM  
VKEQEETIQRIDENVLGAQLDVEAAHSEILKYFQSVTSNRWLMVKIFLILIVFFIIFVVFLA

SEQ ID No:153

MAAGTSSYWEDLRKQARQLENELDLKLVSFSLKCTSYSHSSTRDGRRDRYSSDTPPLL  
NGSSQDRMFETMAIEIEQLLARLTGVNDKMAEYTNAGVPSLNAALMHTLQRHRDILQV  
IYWARDVFIITGVWVFFFNPCIGYVHIYKLGQREKSEKINAMLKGLVLLFFGVTIKF

SEQ ID No:154

MAGRSMQAARCPTDELSLTNCSVVNEKDFQSGQHVVIRTSPNHRYTFTLKTHPSVVP  
SIAFSLPQRKWAGLSIGQEIEVSLYTFDKAKQCIGTMTIEIDFLQKKSNDSPYDTPDKMAA  
EFIQQFNQAYSVGQQLVFSFNEKLFGLLVKDIESMDPSILKGEPATGKRQKIEVGLVVG  
NSQVAFKAENSSLNLIGKAKTKENRQSIINPDWNFEKMGIGGLDKEFSDIFRRAFAFRV  
FPPEIVEQMGCIHVKGILLYGPPGCGKTLLARQIGKMLNAREPKVVNGPEILNKYVGESE  
ANIRKLFADAEERRLGANSGLHIIIFDEIDAICKQRGSMAGSTGVHDTVVNQLLSKIDG  
VEQLNNILVIGMTNRPDIDEALLRPGRLEVKMEIGLPDEKGRQLIHIHTARMRGHQLLS  
ADVDIKELAVETKNFSGAELEGLVRAAQSTAMNRHIKASTKVEVDMEKAESLQVTRGDF  
LASLENDIKPAFGTNQEDYASYIMNGIIKWGDPVTRVLDDGELLVQQTKNSDRTPLVSVL  
LEGPPHSGKTALAAKIAEESNFPFIKICSPDKMIGFSETAKCQAMKKIFDDAYKSQLSCVV  
VDDIERLLDYVPIGPRFSNLVLQALLVLLKKAPPQGRKLLIIGTTSRKDVLQEMEMLNAFS  
TTIHVPNIATGEQLLEALELLGNLKDERTTIAQQVKGKKVWIGIKLLMLIEMSLQMDPE  
YRVRKFLALLREEGASPLDFD

SEQ ID No:155

MAGGRATAAAAASIRERQTVALKRMLNFNVPHIKNSTGEPVWKVLIYDRFGQDIISPLLSV  
KELRDMGITLHLLLHSDRDPIDVPAVYFVMPTEENIDRMCDLRNQLYESYYLNFISAIS  
RSKLEDIANAALELSAVTQVAKVFDQYLNFTLEDDMFVLCNQNKELVSYRAINRPDITDT

EMETVMDTIVDSLFCFYGTLGAVPIIRCSRGTAEMVAVKLDKKLRENLRDARNSLFTG  
DTLGAGQFSFQRPLLVLVDRNIDLATPLHHTWTYQALVHDVLDLHNRVNLEESSGVEN  
SPAGARPKRKNKKSYSDLTPVDKFWQKHKGSPFPEVAESVQQELESYRAQEDEVKRLK  
SIMGLEGEDEGAISMLSDNTAKLTSVSSLPELLEKKRLIDLHTNVATAVLEHIKARKLDV  
YFEYEEKIMSKTTLDKSLLDIISDPDAGTPEDKMRLFLIYYISTQQAPSEADLEQYKKALT  
DAEMNLNPLQYIKQWKAFTKMASAPASYGSTTTKPMGLLSRVMNTGSQFVMEGVKNL  
VLKQQNLVPVTRILDNLMEMKSNPKLDDYRYFDPKMLRGNDSSVPRNKNPFQEAIQVQV  
GGGNYIEYQNLVDYIKGKQKGKILYGCSELFNATQFIKQLSQLGQK

SEQ ID No:156

MSFLIDSSIMITSQILFFGFGWLFFMRQLFKDYEIRQYVVQVIFSVTFAFSCTMFELIIFEIL  
GVLNSSSRYFHWKMNLVILLVFMVFPYIGYFIVSNIRLLHKQRLLFSCLLWLTFFMYFF  
WKLGDPPILSPKHGILSIEQLISRVGVIGVTLMALLSGFGAVNCPYTYMSYFLRNVTDTD  
ILALERRLLQTMDMIISKKKRMAMARRTMFQKGEVHNKPSGFWGMIKSVTTSASGSENL  
TLIQQEVDALIELSRQLFLETADLYATKERIEYSKTFKGKYFNFLGYFFSIYCVWKIFMATI  
NIVFDRVGKTDVTRGIEITVNYLGIQFDVKFWSQHISFILVGIIIVTSIRGLLITLTKFFYAI  
SSKSSNVIVLLAQIMGMYFVSSVLLIRMSMPLEYRTIITEVLGELQFNFYHRWFDVIFLVS  
ALSSILFLYLAHKQAPEKQMAP

SEQ ID No:157

MRSPATGVPLPTPPPLLLLLLLLLPPPLLGDQVGPCRSLSRGRGSSGACAPMGWLC  
PSSASNLWLYTSRCRDAGTELTHGLVPHHDGLRVWCPESEAHIPPAPEGCPWSCR  
LLGIGGHLSPQGKLTLP EEHPCLKAPRLRCQSCKLAQAPGLRAGERSPEESLGGRKR  
NVNTAPQFQPPSYQATVPENQAPGTPVASLRAIDPDEGEAGRLEYTMDALFDSRSNQF  
FSLDPVTGAVTTAEELDRETKSTHVFRVTAQDHGMPRRSALATLTILVTDNDHDPVFE  
QQEYKESLRENLEVGYEVLTVRATDGDAPPNANILYRLLEGSGGSPSEVFEIDPRSGVI  
RTRGPVDREEVESYQLTVEASDQGRDPGPRSTTA AVFLSVEDDNDNAPQFSEKRYVV  
QVREDVTPGAPVLRVTASDRDKGSNAVHYSIMSGNARGQFYLDAQTGALDVVSPLDY  
ETTKEYTLRVRAQDGGRPPLSNVSGLVTVQVLDINDNAPIFVSTPFQATVLESVPLGYLV  
LHVQAIDADAGDNARLEYRLAGVGHDFFPTINNGTGWISVAAELDREEVDFYSFGVEAR  
DHGTPALTASASVSVTVLDVNDNNPTFTQPEYTVRLNEDAAVGTSVVTVSAVDRDAHS  
VITYQITSGNTRNRFSITSQSGGGLVSLALPLDYKLERQYVLAVTASDGTRQDTAQIVVN  
VTDANTHRPVFQSSHYTVNVNEDRPAGTTVVLISATDEDTGENARITYFMEDSIPQFRID  
ADTGAVTTQAELDYEDQVSYTLAITARDNGIPQKSDTTYLEILVNDVNDNAPQFLRDSYQ

GSVYEDVPPFTSVLQISATDRDSGLNGRVFYTFQGGDDGDGDFIVESTSGIVRTLRRRLD  
 RENVAQYVLRAYAVDKGMPPARTPMEVTVTVLDVNDNPPVFEQDEFDVFVEENSPIGL  
 AVARVTATDPDEGTNAQIMYQIVEGNIPEVFQLDIFSGELTALVDLDYEDRPEYVLVIQAT  
 SAPLVSRATVHVRLLDRNDNPPVLGNFEILFNHYVTNRSSSFPGGAIGRVP AHDPDISD  
 SLTYSFERGNELSLVLLNASTGELKLSRALDNNRPLEAIMSVLVSDGVHSVTAQCALRVT  
 IITDEMLTHSITLRLEDMSPERFLSPLLGLFIQAVAATLATPPDHVVVFVNVQRD TDAPGGH  
 ILNVSLSVGQPPGPGGGPPFLPSEDLQERLYLNRSLLTAISAQRVLPFDDNICLREPCEN  
 YMRCSVSVLRFDSSAPFIASSSVLFRPIHPVGGLRCRCPPGFTGDYCETEVDLCYSRPCG  
 PHGRCRSREGGYTCLCRDGYTGEHCEVSARSGRCTPGVCKNGGTCVNLLVGGFKCD  
 CPSGDFEKPYPYCQVTTRSFP AHSFITFRGLRQRFHFTLALS FATERDGLLLYNGRFNEK  
 HDFVALEVIQEQQVQLTFSAGESTTTVSPFVPGGVSDGQWHTVQLKYYNKPLL GQTGLP  
 QGPSEQKVAVVTVDGCDTGVALRFGSVLGNYS CA AQGTQGGSKKSLDLTG PLLGGV  
 PDLPE SFPVRMRQFVGCMRNLQVDSRHIDMADFIANN GTVPGCPAKKNVCDSNTCHN  
 GGTCVNQWDAFSCECPLGFGGKSCAQEMANPQHFLGSSLVAWHGLSLPISQPWYLSL  
 MFRTRQADGVLLQAITRGRSTITLQLREGHVMLSVEGTGLQASSLRLEPGRANDGDWH  
 HAQLALGASGGPGHAILSFDYGGQRAEGNLGPRLHGLHLSNITVGGIPGPAGGVARGF  
 RGCLQGVRVSDTPEGVNSLDPSHGESINVEQGC SLPDPCDSNPCPANSYCSNDWDSY  
 SCSCDPGYYGDNCTNVCDLNPCEHQSVCTRKPSAPHGYTCECPPNYLGPYCETRIDQ  
 PCPRGWWGHPTCGPCNCDVSKGFDPDCNKTSGECHCKENHYRPPGSPTCLLCDCYP  
 TGSLSRVCDPEDGQCPCPKPGVIGRQC DRCDNPFAEVT TNGCEVNYDSCPRAIEAGIW  
 WPRTRFGLPAAAPCPKGSFGTAVRHCD EHRGWLPPNLFNCT SITFSELKGFAERLQRN  
 ESGLD SGRSQQLALLLRNATQHTAGYFGSDVKVAYQLATRLLAHESTQRGFGLSATQD  
 VHFTENLLRVGSALLDTANKRHWELIQQT EGGTAWLLQH YEAYASALAQNM RHTYLSP  
 FTIVTPNIVISVVRLDKGNFAGAKLP RYEALRGEQPPDLETTVILPESVFRET PPVVRPAG  
 PGEAQEPEELARRQRRHPELSQGEAVASV IYRTLAGLLPHNYDPDKRSLRVPKRPIINT  
 PVVSISVHDDEELLPRALDKPVT VQFRLL ETEERTKPICVFWNHSILVSGTGGWSARGC  
 EVVFRNESHVSCQCNHMTSFAVLMDVSRREN GEILPLKTLTYVALGVT LAALLTFFFLT  
 LLRILRSNQHGIRRNLTAA LGLAQLVFL LGINQADLPFACTVIAILLHFLYLCTFSWALLEAL  
 HLYRALTEVRDVNTGPMRFYYMLGWGVPAFITGLAVGLDPEGYGNPDFCWLSIYDTLI  
 WSFAGPVAFVSM SVFLYILAA RASCAAQRQGF EKKG PVSGLQPSFAVLLLLSATWLLA  
 LLSVNSDTLLFH YLFATCNCIQGPFIFLSYV VLSKEVRKALKLACSRKPSPDPALTTKSTL  
 TSSYNCPSPYADGRLYQPYGDSAGSLHSTSRSGKSQPSYIPFLLREESALNPGQGPPG  
 LGDPGSLFLEGQDQHQHDPD TDSDS DLSLEDDQSGSYASTHSSDSEEEEEEEEEEEA AF  
 PGEQGWDSLLGPGAERLPLHSTPKDGGPGPGKAPWPGDFGT TAKESSGNGAPEERL



RENGDALSREGSLGPLPGSSAQPHKGILKKKCLPTISEKSSLLRPLEQCTGSSSRGSSA  
SEGSRRGGPPPRPPPRQSLQEQLNGVMPIAMSIKAGTVDEDEDSSGSEFLFFNFLH

SEQ ID No:158

MLRRPAPALAPAARLLLGLLCGGGVWAARVNVKHKPWLEPTYHGIVTENDNTVLLDPP  
LIALDKDAPLRFAESFEVTVTKEGEICGFKIHGQNVPFDAVVVDKSTGEGVIRSKEKLDC  
ELQKDYSFTIQAYDCGKGPDGTNVKKSHKATVHIQVNDVNEYAPVFKEKSYKATVIEGK  
QYDSILRVEAVDADCSPQFSQICSYEIITPDVPFTVDKDGYIKNTEKLNKGKEHQYKLTVT  
AYDCGKKRATEDVLVKISIKPTCTPGWQGWNNRIEYEPGTGALAVFPNIHLETCDPVA  
SVQATVELETSHIGKGCDDRTYSEKSLHRLCGAAAGTAELLPSPSGSLNWTMGLPTDN  
GHSDSQVFEFNGTQAVRIPDGVVSVSPKEPFTISVWMRHGPFGRKKETILCSDKTD  
NRHHYSLYVHGCRLIFLRQDPSEEKKYRPAEFHWKLNQVCDEEWHHYVLNVEFPSVT  
LYVDGTSHEPFSVTEDYPLHPSKIETQLVVGACWQEFSGVENDNETEPVTVASAGGDL  
HMTQFFRGNLAGLTLRSGKLADKKVIDCLYTCKEGLDLQVLEDSEGRGVQIQAHPSQLVL  
TLEGEDLGELDKAMQHISYLSNRQFPTPGIRRLKITSTIKCFNEATCISVPPVDGYVMVLQ  
PEEPKISLSGVHHFARAASEFESSEGVFLFPELRIISTITREVEPEGDGAEDPTVQESLVS  
EEIVHDLDTCEVTVEGEELNHEQESLEVDMARLQQKGIEVSSSELGMTFTGVDTMASY  
EEVLHLLRYRNWHARSLLDRKFKLICSELNGRYSNEFKVEVNVIHTANPMEHANHMAA  
QPQFVHPEHRSFVDLSGHNLANPHPFVAVPSTATVVIVVCVSFLVFMILGVFRIRAAHR  
RTMRDQDTGKENEMDWDDSAITITVNPMEITYEDQHSSEEEEEEEEEEESEEDGEEDD  
ITSAESESSEEEEGEQGDPQNATRQQQLEWDDSTLSY

SEQ ID No:159

MGKGGNQGEAAEREVSVPFTSWEEIQKHNLRTRDWLVIDRKVYNITKWSIQHPGGQ  
RVIGHYAGEDATDAFRAFHPDLEFVGKFLKPLLIGELAPEEPSQDHGKNSKITEDFRALR  
KTAEDMNLFKTNHVFFLLLLAHIIALESIAWFTVFYFGNGWIPTLITAFVLATSQAQAGWL  
QHDYGHLSVYRKPKWNHLVHKFVIGHLKGASANWWNHRHFQHHAKPNIFHKDPDVNM  
LHVFLGGEWQPIEYGKKKLKYLPHNHQHEYFFLIGPPLLIPMYFYQYQIIMTMIVHKNWVDL  
AWAVSYYIRFFITYIPFYGILGALLFLNFIRFLESHWFVWVTQMNHIVMEIDQEAYRDWFS  
SQLTATCNVEQSFFNDWFSGHLNFQIEHHLFPTMPRHNHLHKIAPLVKSLCAKHGIEYQE  
KPLLRALLDIIRSLKKSGKLWLDAYLHK

SEQ ID No:160

MTATEALLRVLLLLLAFGHSTYGAECFPACNPQNGFCEDDNVCRCQP GWQGPLCDQC  
VTSPGCLHGLCGEPGQCICTDGWDGELCDRDVRACSSAPCANNGTCVSLDGGLYECS  
CAPGYSGKDCQKKDGPVINGSPCQHGGTCVDDEGRASHASCLCPPGFSGNFCEIVA  
NSCTPNPCENDGVCTDIGGDFRCRCPAGFIDKTC SRPVTNCASSPCQNGGTCLQHTQ  
VSYECLCKPEFTGLTCVKKRALSPQQVTRLPSGYGLAYRLTPGVHELPVQQPEHRILKV  
SMKELNKKTPLLTEGQAICFTILGVLTSLVVLGTVGIVFLNKCETWVSNLRYNHMLRKKK  
NLLLQYNSGEDLAVNIIFPEKIDMTTFSKEAGDEEI

SEQ ID No:161

MELHYLAKKSNQADLCDARDWSSRGLPGDQADTAATRAALCCQKQCASTPRATEME  
GSKLSSSPASPSSSLQNSTLQPD AFPPGLLHSGN NQITAERKVCNCCS QELET SFTYVD  
KNINLEQRNRSSPSAKGHNHPGELGWENPNEWSQEA AISLISEEEDDT SSEATSSGKSI  
DYGFISAILFLVTGILLVIISYIVPREVTVD PNTVAAREMERLEKESARLGAHLDR CVIAGLC  
LLTLGGVILSCLLMMSMWKGELYRRNRFASSKESAKLYGSFNFRMKTSTNENTLELSLV  
EEDALAVQS

SEQ ID No:162

MAPRPLGPLVLALGGAAVLG SVLFILWKTYFGRGRERRWDRGEAWWGAE AARLPE  
WDEWDPEDEEDEEPAL EEELEQREVLVLGLDGAGKSTFLRVLSGKPPLEGH IPTWGFNS  
VRLPTKDFEVDLLEIGGSQNLRFYWKEFVSEVDVLV FVVD SADRRLRPWARQELHKLLD  
KDPDLPVVVVANKQDLSEAMSMGELQRELGLQAIDNQREVFLLAASIAPAGPTFE EPGT  
VHIWKLLLELLS

SEQ ID No:163

MSDSGSQLGSMGSLTMKSQLQITVISAKLKENKKNWFGPSPYVEVTVDGQSKKTEKCN  
NTNSPKWKQPLTVIVTPVSKLHFRVWSHQ TLKSDVLLGTAALDIYETLKSNNMKLEEVV  
VTLQLGGDK EPTETIGDLSICLDGLQLESEVV TNGETTCS ENGVSLCLPRLECNSA ISAH  
CNLCPLGLSDSPISASRVAGFTGASQNDDGSR SKDETRVSTNGSDDPEDAGAGENRR  
VSGNNSPSLSNGGFKPSRPPRPSRPPPTPRRPASVNGSPSATSESDGSSTGSLPPT  
NTNTNTSEGATSGLIPLTISGGSGPRPLNPVTQAPLPPGWEQRVDQHGRVYYVDHVEK  
RTTWDRPEPLPPGWERRVDNMGRIYYVDHFTRTTTWQRPTLESVRNYEQWQLQRSQ  
LQGAMQQFNQRFIYGNQDLFATSQSKEFDPLGPLPPGWEKRTDSNGRVYFVNHNTRIT  
QWEDPRSQQQLNEKPLPEGWEMRFTVDGIPYFVDHNRRTTTYIDPRTGKSALDNGPQI  
AYVRDFKAKVQYFRFWCQQLAMPQH IKITVTRKTLFEDSFQQIMSFSPQDLRRRLWVIF

PGEEGLDYGGVAREWFFLLSHEVLNPMYCLFEYAGKDNVCLQINPASYINPDHLKYFRF  
IGRFIAMALFHGKFIDTGFSLPFYKRILNKPVGLKDLESIDPEFYNSLIWVKENNIEECDLE  
MYFSVDKEILGEIKSHDLKPNGGNILVTEENKEEYIRMVAEWRLSRGVVEEQTAFFEGF  
NEILPQQYLQYFDAKELEVLLCGMQEIDLNDWQRHAIYRHYARTSKQIMWFWQFVKEID  
NEKRMRLQLQFVTGTCRLPVGGFADLMGSNGPQKFCIEKVGKENWLPRSHTCFNRLDL  
PPYKSYEQLKEKLLFAIEETEGFGQE

SEQ ID No:164

LQLSVKMSVLISQSVINYVEEENIPALKALLEKCKDVDERNECGQTPLMIAAEQGNLEIVK  
ELIKNGANCNLEDLDNWTALISASKEGHVHIVEELLKCGVNLEHRDMGGWTALMWACY  
KGRTDVVELLLSHGANPSVTGLYSVYPIIWAAGRGHADIVHLLLQNGAKVNCSDKYGTT  
PLVWAARKGHLECVKHLLAMGADV DQEGANSMTALIVAVKGGYTQSVKEILKRNPVN  
LTDKDGNTALMIASKEGHTEIVQDLLDAGTYVNIPDRSGDTVIGAVRGGHVEIVRALLQ  
KYADIDIRGQDNKTALYWAVEKGNATMVRDILQCNPDTEICTKDGETPLIKATKMRNIEV  
VELLLDKGAKVSAVDKKGDTPLHIAIRGRSRKLAELLRNPKDGRLLYRPNKAGETPYNI  
DCSHQKSILTQIFGARHLSPTETDGDMLGYDLYSSALADILSEPTMQPPICVGLYAQWG  
SGKSFLKKLEDEMKTFFAGQQIEPLFQFSWLIVFLTLLLCGGLGLLFAFTVHPNLGIAVSL  
SFLALLYIFFIVIYFGGRREGESWNWAWVLSTRLARHIGYLELLLKLMFVNPPPELPEQTTK  
ALPVRFLFTDYNRLSSVGGETSLAEMIATLSDACEREFGLATRLFRVFKTEDTQGKKK  
WKKTCCLPSPFVIFLFIIGCIISGITLLAIFRVDPKHLTVNAVLIASVVGLAFVLNCRWWQ  
VLDSLLNSQRKRLHNAASKLHKLKSEGFMKVLKCEVELMARMAKTIDSFTQNQTRLVVII  
DGLDACEQDKVLQMLDTRVFLFSKGPFIASFDPHIIKAINQNLNSVLRDSNINGHDYM  
RNIVHLPVFLNSRGLSNARKFLVTSATNGDVPCSDTTGIQEDADRRVSQNSLGEMTKLG  
SKTALNRRDTRRRQMQRITRQMSFDLTKLLVTEWDFSDISPQTMRRLLNIVSVTGRL  
LRANQISFNWDRLASWINLTEQWPYRTSWLILYLEETEGIPDQMTLKTIERISKNIPTTK  
DVEPLLEIDGDIRNFEVFLSSRTPVLVARDVKVFLPCTVNLDPKLREIIADVRAAREQISIG  
GLAYPPLPLHEGPPRAPSGYSQPPSVCSSTSFNGPFAGGVVSPQPHSSYSGMTGPQ  
HPFYNRPFAPYLYTPRYYPGGSQHLISRPSVKTS�PRDQNNGLEVIKEDAAEGLSSPT  
DSSRGSGPAPGPVLLNSLNVDACEKLKQIEGLDQSMPLQYCTTIKKANINGRVLAQC  
NIDELKKEMNMNFGDWHLFRSTVLEMRNAESHVVPEDPRFLSESSSGPAPHGEPARR  
ASHNELPHTELSSQTPYTLNFSFEELNTLGLDEGAPRHSNLSWQSQTRRTPSLSSLNS  
QDSSIEISKLTDKVQAEYRDAYREYIAQMSQLEGGPGSTTISGRSSPHSTYYMGQSSSG  
GSIHSNLEQEKGKDSEPKPDDGRKSFLMKRGDVIDYSSSGVSTNDASPLDPITEEDEKS  
DQSGSKLLPGKKSSERSSLFQTDLKLKGSGLRYQKLPSDEDESGTEESDNTPLLKDDK

DRKAEGKVERVPKSPEHSAEPIRTFIKAKEYLSDALLDKKDSSDSGVRSSSESSPNHSLH  
 NEVADDSQLEKANLIELEDDSHSGKRGIPHSLSGLQDPIIARMSICSEDKKSPSECSLIAS  
 SPEENWPACQKAYNLNRTSTVTLNNSAPANRANQNFDMEGIRETSQVILRPSSSP  
 NPTTIQENENLKSMTHKRSQRSSYTRLKDPPELHAAASSESTGFGEERESIL

SEQ ID No:165

MATAGGGSGADPGSRGLLRLLSFCVLLAGLCRGNSVERKIYIPLNKTAPCVRLLNATHQI  
 GCQSSISGDTGVIHVVEKEEDLQWVLTGDPNPPYMVLLSKHFTRDLMEKLGRTSRIA  
 GLAVSLTKPSPASGFSPSVQCPNDGFGVYSNSYGPEFAHCREIQWNSLGNGLAYEDFS  
 PFIILLEDENETKVIKQCYQDHNLSQNGSAPTFLCAMQLFSHMHAVISTATCMRRSSIQ  
 STFSINPEIVCDPLSDYNVWSMLKPINTTGTLKPDDRVAATRLDSRSFFWNVAPGAE  
 SAVASFVTQLAAAEALQKAPDVTTLPRNVMFVFFQGETFDYIGSSRMVYDMEKGKFPV  
 QLENVDSFVELGQVALRTSLELWMHTDPVSQKNESVRNQVEDLLATLEKSGAGVPAVI  
 LRRPNQSQPLPPSSLQRFLRARNISGVVLADHSGAFHNKYYQSIYDTAENINVSYPEWL  
 SPEEDLNFVTD TAKALADVATVLGRALYELAGGTNFSDTVQADPQTVTRLLYGFLIKAN  
 NSWFQSILRQDLRSYLG DGPLQHYIAVSSPTNTTYVVQYALANLTGTVVNLTREQCQDP  
 SKVPSSENKDLYEYSWVQGPLHSNETDRLPRCVRSTARLARALSPAFELSQWSSTEYST  
 WTESRWKDIRARIFLIASKELELITLVGFGILIFSLIVTYCINAKADVLFIAPREPGAVSY

SEQ ID No:166

MEDLDQSPVLVSSSDSPPRPQPAFKYQFVREPEDEEEEEEEEEDEDEDLEELEVLERK  
 PAAGLSAAPVPTAPAAGAPLMDFGND FVPPAPRGPLPAAPPVAPERQPSWDPSPVSS  
 TVPAPSPLSAAAVSPSKLPEDDEPPARPPPPPPASVSPQAEPVWTPPAPAPAAPPSTP  
 AAPKRRGSSGSVDETLFALPAASEPVIRSSAENMDLKEQPGNTISAGQEDFPSVLLETA  
 ASLPSLSPLSAAASFKEHEYLGNLSTVLPTEGTLQENVSEASKEVSEKAKTLLIDRDLTEF  
 SELEYSEMGSFSVSPKAESAVIVANFREEIIVKNKDEEEKLVSNILHNQQELPTALTKL  
 VKEDEVVSSEKAKDSFNEKRVAVEAPMREEYADFKPFERVWEVKDSKEDSDMLAAGG  
 KIESNLESKVDDKKCFADSLEQTNHEKDSESSNDDTSFPSTPEGIKDRSGAYITCAPFNPA  
 ATESIATNIFPLLGDPTSENKTDEKKIEEKKAQIVTEKNTSTKTSNPFLVAAQDSETDYVT  
 TDNLTKVTEEVVANMPEGLTPDLVQEACESELNEVTGTKIAYETKMDLVQTSEVMQESL  
 YPAAQLCPSFEESEATPSPVLPDIVMEAPLNSAVPSAGASVIQPSSSPLEASSVNYESIK  
 HEPENPPPYEEAMSVSLKKVSGIKEEIKEPENINAALQETEAPYISACDLIKETKLSAEP  
 PDFSDYSEMAKVEQPVPDHSELVEDSSPDSEPVDLFSDDSIPDVPQKQDETVMVLKES  
 LTETSFESMIEYENKEKLSALPPEGGKPYLESFKLSLDNTKDTLLPDEVSTLSKKEKIPLQ

MEELSTAVYSNDDLFISKEAQIRETETFSOSSPIEIIDEFPTLISSKTDSFSKLAREYTDLEV  
SHKSEIANAPDGAGSLPCTELPHDLSLKNIQPKVEEKISFSDDFSKNGSATSXVLLLPPD  
VSALATQAEIESIVKPKVLVKEAEKKLPSTTEKEDRSPSAIFSAELSKTSVVDLLYWRDIK  
KTGVVFGASLFLLLSLTVFSIVSVTAYIALALLSVTISFRIYKGVIAIQKSDEGHPPFRAYLE  
SEVAISEELVQKYSNSALGHVNCTIKELRRLFLVDDLVDLSKFAVLMWVFTYVGALFNGL  
TLLILALISLFSVPVIYERHQAQIDHYLGLANKNVKDAMAKIQAKIPGLKRKAE

SEQ ID No:167

MRLPGAMPALALKGELLLLSELLLEPQISQGLVVTTPGPELVNLVSSTFVLTCSGSAPV  
VWERMSQEPPQEMAKAQDGTFSVLTLTNLTGLDTGEYFCTHNSRGLETDERKRLYI  
FVPDPTVGFLPNDAEELFIFLTEITEITIPCRVTDPLVVTLEKKGDVALPVPYDHQGRF  
SGIFEDRSYICKTTIGDREVSDAYYVYRLQVSSINVSNAVQTVVRQGENITLMCIVIGN  
EVVNFETYPRKESGRLVEPVTDFLDMPYHIRSILHIPSAAELEDSTYTCNVTESVNDH  
QDEKAINITVVESGYVRLLEGEVGTQLQFAELHRSRTLQVVFAYPPPTVLWFKDNRTLGD  
SSAGEIALSTRNVSETRYVSELTIVRVKVAEAGHYTMRAFHEDAEVQLSFQLQINVPVR  
VLELSESHPDSGEQTVRRCRGRGMPQPNIIWSACRDLKRCPRELPPTLLGNSSEEEESQL  
ETNVTYWEEEEEQEFVVSTLRLQHVDRLPSVRCTLRNAVGGDTQEVIVPHSLPFKVVVI  
SAILALVVLTIISLIILIMLWQKKPRYEIRWKVIESVSSDGHEYIYVDPMLPYDSTWELPR  
DQLVLGRTLGSAGFGQVVEATAHGLSHSQATMKVAVKMLKSTARSSSEKQALMSELKIM  
SHLGPLHNLVNNLLGACTKGGPIYIITEYCRYGDLVDYLHRNKHTFLQHHSDKRRPPSAEL  
YSNALPVGLPLPSHVSLTGESDGGYMDMSKDESVDYVPMMLDMKGDVKYADIESSNYM  
APYDNYVPSAPERTCRATLINESPVLSYMDLVGFSYQVANGMEFLASKNCVHRDLAAR  
NVLICEGKLVKICDFGLARDIMRDSNYISKGSTFLPLKWMAPESIFNSLYTTLSDVWSFGI  
LLWEIFTLGGTPYPELPMNEQFYNAIKRGYRMAQPAHASDEIYEIMQKCWEEKFEIRPP  
FSQLVLLLERLLGEGYKKKYQQVDEEFLRSDHPAILRSQARLPGFHGLRSPLDTSSVLY  
TAVQPNEGDNNDYIIPDPKPEVADEGPLEGSPSLASSTLNEVNTSSTISCDSPLEPQDE  
PEPEPQLELQVEPEPELEQLPDSGCPAPRAEAEDSFL

SEQ ID No:168

MGAARGSPARPRRLPLLSVLLLPLGGTQTAIVFIKQPSSQDALQGRRALLRCEVEAPG  
PVHVVWLLDGAPVQDTERRFAGSSLSFAAVDPLQDSGTFQCVARDDVTGEEARSAN  
ASFNIKWIEAGPVVLKHPASEAEIQPQTQVKLRCHIDGHPRPTYQWFRDGTPLSDGQSN  
HTVSSKERNLTLRPAGPEHSGLYSCCAHSASFQACSSQNFTLSIADESFAVVVLAPQDV  
VVARYEEAMFHCQFSAQPPPSLQWLFEDETPITNRSRPPHLRRATVFANGSLLLTQVR

PRNAGIYRCIGQGQRGPPPIILEATLHLAEIEDMPLFEPRVFTAGSEERTVCLPPKGLPEPS  
VWWEHAGVRLPTHGRVYQKGHELVLANIAESDAGVYTCHAANLAGQRRQDVNITVAT  
VPSWLKKPQDSQLEEGKPGYLDCLTQATPKPTVWYRNQMLISEDSEFEVFKNGTLRI  
NSVEVYDGTWYRCMSSTPAGSIEAQAVLQVLEKLKFTPPPQPQQCMGFDKEATVPCS  
ATGREKPTIKWERADGSSLPEWVTDNAGTLHFARVTRDDAGNYTCIASNGPQQGQIRAH  
VQLTVAVFITFKVEPERTTVYQGHTALLQCEAQGDPKPLIQWKGKDRILDPTKLGPRMHI  
FQNGSLVIHDVAPEDSGRYTCIAGNSCNIKHTEAPLYVVDKPVPEESEGGSPPPYKMI  
QTIGLSVGAAYIIAVLGLMFYCKKRCKAKRLQKQPEGEEPEMECLNGGPLQNGQPS  
AEIQEEVALTSLGSGPAATNKRHSTSDKMHFPRSSLQPITTLGKSEFGEVFLAKAQGLE  
EGVAETLVLVKSLSQSKDEQQQLDFRRELEMFGKLNHANVVRLGLCREAEPHYMVLEY  
VDLEDLKQFLRISKSKDEKLKSQPLSTKQKVALCTQVALGMEHLSNNRFVHKDLAARNC  
LVSAQRQVKVSALGLSKDVYNSEYYHFRQAWVALRWMSPEAILEGDFSTKSDVWASG  
VLMWEVFTHGEMPHGGQADDEVLDLQAGKARLPQPEGCPKLYRLMQRCWALSPK  
DRPSFSEIASALGDSTVDSKP

SEQ ID No:169

MPSSVSWGILLLAGLCCLVPVSLAEDPQGDAQAQKTDTSHHDDQDHPTFNKITPNLAEFAF  
SLYRQLAHQSNSTNIFFSPVSIATAFAMLSLGTKADTHDEILEGLNFNLTETPEAQIHEGF  
QELLRTLNPDSQLQLTTGNGLFLSEGLKLVDFLEDVKKLYHSEAFTVNFGDTEEAKE  
QINDYVEKGTQGKIVDLVKELDRDTVFALVNYIFFKGKWERPFEVKDTEEEEDFHVDQVT  
TVKVPMMKRLGMFNIQHCKKLSSWVLLMKYLG NATAIFFLPDEGKLQHLENELTHDIITK  
FLENEDRRSASLHLPKLSITGTYDLKSVLGQLGITKVFSGADLSGVTEEAPLKLSKAVH  
KAVLTIDEKGTAAAGAMFLEAIPMSIPPEVKFNKPFVFLMIEQNTKSPLFMGKVVNPTQK

SEQ ID No:170

MVSIPEYYEGKNVLLTGATGFLGKVLLEKLLRSCPKNVSVYVLVRQKAGQTPQERVEEV  
LSGKLFDRLRDENPDFREKIIAINSELTQPKLALSEEDKEVIDSTNIIFHCAATVRFNENLR  
DAVQLNVIATRQLILLAQQMKNLVFMHVSTAYAYCNRKHIDEVVYPPVPDPKKLIDSLE  
WMDDGLVNDITPKLIGDRPNTYIYTKALAEYVVQQEGAKLNVAIVRPSIVGASWKEPFPG  
WIDNFNGPSGLFIAAGKGILRTIRASNNALADLVVDVVVNMSLAAAWYSGVNRPRNIM  
VYNCTTGSTNPFHWGEVEYHVISTFKRNPLEQAFFRRPNVNLTSNHLLYHYWIAVSHKAP  
AFLYDIYLRMTGRSPRCPSPFKFNSNSLSHHYRKGVSHRVSALLLDCTHVDRSETATFNI  
DVRQLHWAIEYIENYCLGTTKYVLNEEMSGLPAARKHLNKTLSLFTALCHGKLTFFVDD  
TFGFPCLLASGGPLLSVSLHFSAYVYSQIHLAFILRDLGSHSAPSLASLAGPRELTVGSLL

DREWRQIKTDDFELGKSAGEVDLEGADIEGCLLATSPAVRQQALLQRGVQWYISIPTTQ  
ETVAMEMQI

SEQ ID No:171

MATRSSRRESRLPFLFTLVALLPPGALCEVWTQRLHGGSAPLPQDRGFLVVQGDPREL  
RLWARGDARGASRADEKPLRRKRSAALQPEPIKVYGVVSLNDSHNQMVVHWAGEKS  
NVIVALARDSLALARPSSDVVYSYDYGKSFKKISDKLNFGGLNRSEAVIAQFYHSPADN  
KRYIFADAYAQYLWITDFCNTLQGFSIPFRAADLLLHASKASNLLGLFDRSHPNKQLWKS  
DDFGQTWIMIQEHVKSFSWGIDPYDKPNTIYIERHEPSGYSTVFRSTDFQSSRENQEVIL  
EEVRDFQLRDKYMFATKVHLLGSEQQSSVQLWVSFGRKPMRAAQFVTRHPINEYYIA  
DASEDQVFVVCVSHSNNRTNLYISEAEGKFSLSLENVLYYSPGGAGSDTLVRYFANEPP  
ADFHRVEGLQGVIATLINGSMNEENMRSVITFDKGGTWEFLQAPAFGTGYGEKINCELS  
QGCSLHLAQRLSLLNLQLRRMPILSKESAPGLIATGSVGKNLASKTENVYISSAGARW  
REALPGPHYTTWGDHGGIITAIAQGMETNELKYSTNEGETWKTFFSEKPVFVYGLLTP  
GEKSTVFTIFGSNKENVHSLILQVNATDALGVPCTENDYKLWSPSDERGNELGLHK  
TVFKRRTPHATCFNGEDFDRPVVVSNCSCSTREDYECDFGFKMSEDLSLEVCVPDPFEFS  
GKSYSPVPCPVGSTYRRTRGYRKISGDTCSGGDVEARLEGELVPCPLAEENEFILYAV  
RKSIYRYDLASGATEQLPLTGLRAAVALDFDYEHNCLYWSDALDVIQRLCLNGSTGQE  
VIINSGLETVEALAFEPLSLLYVWDAGFKKIEVANPDGDFRLTIVNSSVLDRPRALVLP  
QEGVMFWTDWGDLPKGIYRSNMDGSAAYHLVSEDVKWPNGISVDDQWIYWTDAYLE  
CIERITFSGQQRSVILDNLPHPYAIAVFKNEIYWDDWSQLSIFRASKYSGSQMEILANQLT  
GLMDMKIFYKGNKTSNACVPRPCSLCLPKANNRSRSCRPEDVSSSVLPSGDLMCD  
CPQGYQLKNNTCVKEENTCLRNQYRCSNGNCINSIWWCDFDNDGDMSDERNCPPTI  
CDLDTQFRCQESGTCIPLSYKCDLEDDCGDNSDESHCEMHQCRSDEYNCSSGMCIRS  
SWVCDGDNDCRDWSDEANCTAIYHTCEASNQCRNGHCIPQRWACDGDGTDGQDGS  
DEDPVNCEKKCNCFRCPNGTCIPSSKHCDGLRDCSDGSDEQHCEPLCTHFMDFVCKN  
RQQCLFHSMVCDGIIQCRDGSDEDAAFAGCSQDPEFHKVCDEFQFQCQNGVCISLIWK  
CDGMDDCGDYSDEANCENPTEAPNCSRYFQFRCENGHCIPNRWKCDRENDGCDWS  
DEKDCGDSHILPFSTPGPSTCLPNYYRCSSGTCVMDTWVCDGYRDCADGSDEEACPL  
LANVTAASTPTQLGRCDRFEFECHQPKTCIPNWKRCDCGHQDCQDGRDEANCPTHSTL  
TCMSREFQCEGEACIVLSERCDFLDCSDESDEKACSDTLVYKVQNLQWTADFSG  
DVTLTWMRPKKMPASCVYVYRVVGESIWKLTETHSNKTNTVLKVLKPDTTYQVKV  
QVQCLSKAHNTNDFVTLRTPEGLPDAPRNLLSLPREAEGVIVGHWAPPIHGLIREYI  
VEYSRSGSKMWASQRAASNFTKILLVNTLYTVRVAAVTSRGIGNWSDSKSITTIKKGK

VIPPPDIHIDSYGENYLSFTLTMESDIKVNGYVNVNLFWAFDTHKQERRTLNFRGSILSHKV  
 GNLTHTSYEISAWAKTDLGDSPLAFEHVMTRGVRPPAPSLKAKAINQTAVECTWTGP  
 RNVVYGIFYATSFLDLYRNPKSLTTSLHNKTVIVSKDEQYLFLVRVVVPYQGPSSDYVVV  
 KMIPDSRLPPRHLHVHTGKTSVVIKWESPYDSPDQDLLYAIKVDLIRKTDERSYKVKSR  
 NSTVEYTLNKLPGGKYHIIVQLGNMSKDSSIKITTVSLSAPDALKIITENDHVLLFWKSLA  
 LKEKHFNESRGYEIHMFD SAMNITAYLGNTTDNFFKISNLKMGHNYTFTVQARCLFGNQI  
 CGEPAILLYDELGSGADASATQAARSTDVAAVVVPILFLILLSLGVGFAILYTKHRRQLQS  
 FTAFA NSHYSSRLGSAIFSSGDDLGEDDEDAPMITGFSDDVPMVIA

SEQ ID No:172

GRWASGEMAPSGSLAVPLAVLVLLLWGAPWTHGRRSNVRVITDENWRELLEGDWMIE  
 FYAPWCPACQNLQPEWESFAEWGEDLEVNIKVDVTEQPGLSGRFIITALPTIYHCKDG  
 EFRRYQGPRTKKDFINFISDKWKSEIPVSSWFGPGSVLMSSMSALFQLSMWIRTCHN  
 YFIEDLGLPVWGSYTVFALATLFSGLLLGLCMIFVADCLCPSKRRRPQPYPYPSKKLLSE  
 SAQPLKKVEEEEQEAEDEEDVSEEEAESKEGTNKDFPQNAIRQRSLGPSLATDKS

SEQ ID No:173

MVNYAWAGRSQRKLWWRSVAVLTCKSVVRPGYRGGLQARRSTLLKTCARARATAPG  
 AMKMVAPWTRFYNSCCLCCHVRTGTILLGVWYLIINAVVLLILLSALADPDQYNFSSSE  
 LGGDFEFMDDANMCIAIAISLLMILICAMATYGAYKQRAAWIIPFFCYQIFDFALNMLVAIT  
 VLIYPNSIQEYIRQLPPNFPYRDDVMSVNPTCLVLIILLFISIILTFKGYLISCVWNCYRYING  
 RNSSDVLVYVTSNDTTVLLPPYDDATVNGAAKEPPPPYVSA

SEQ ID No:174

MEFYESAYFIVLIPSIVITVIFLFFWLFMKETLYDEVLAQKQREQKLIPTKTDKKKAEEKKN  
 KKKEIQNGNLHESDSESVPDFKLSDALAVEDDQVAPVPLNVVETSSSVRERKKKEKK  
 QKPVLEEQVIKESDASKIPGKKVEPVVTKQPTPPSEAAASKKKPGQKKSKNGSDDQD  
 KKVETLMVPSKRQEALPLHQETKQESGSGKKASSKKQKTENVFVDEPLIHATTYIPLMD  
 NADSSPVVDKREVIDLLKPDQVEGIQKSGTKKLTETDKENAEVKFKDFLLSLKTMMFS  
 EDEALCVVDLLKEKSGVIQDALKKSSKGELTTLIHQLQEKD KLLAAVKEDAAATKDRCKQ  
 LTQEMMTEKERSNVVMTRMKDRIGTLEKEHNVFQNKIHVSQYQETQQMQMKFQQVREQ  
 MEAEIAHLKQENGILRDAVSNTTNQLESKQSAELNKL RQDYARLVNELTEKTGKLQQUEE  
 VQKKNAEQAAATQLKVQLQEAEERRWEEVQSYIRKRTAEHEAAQQDLQSKFVAKENEVQ  
 SLHSKLTDTLVSKQQLEQRLMQLMESEQKRVNKEESLQMQVQDILEQNEALKAQIQQF



HSQIAAQT SASVLA EELHKVIAEKDKQIKQTEDSLASERDRLTSKEEELKDIQNMNFLKA  
EVQKLQALANEQAAAAHELEKMQQSVYVKDDKIRLLEEQLQHEISNKMEEFKILNDQNK  
ALKSEVQKLQTLVSEQPNKDVVEQMEKCIQEKDEKLKTVEELLETGLIQVATKEEELNAI  
RTENSSLTKEVQDLKAKQNDQVSFASLVEELKKVIHEKDGKIKSVEELLEAEELLKVANKE  
KTVQDLKQEI KALKEEIGNVQLEKAQQLSITSKVQELQNLLKGKEEQMNTMKAVLEEKE  
KDLANTGKWLQDLQEENESLKAHVQEV AQHNLKEASSASQFEELEIVLKEKGNELKRLE  
AMLKERESDLSSKTQLLQDVQDENKLFKSQIEQLKQQNYQQASSFPPHEELLKVISERE  
KEISGLWNELDSLKDAVEHQ RKKNNDLREKNWEAMEALASTEKMLQDKVNKTSKERQ  
QQVEAVELEAKEVLKKLFPKVSVP SNLSYGEWLHGFEKKAKECMAGTSGSEEVKVLEH  
KLKEADEMHTLLQLECEKYKSVLAETEGILQKLQRSVEQEENKWKVKVDESHKTIKQMQ  
SSFTSSEQELERLRSENKD IENLRREHLEMELEKAEMERSTYVTEVRELKDLLTELQ  
KKLDDSYSEAVRQNEELNLLKAQLNETLTKLRTEQNERQKVAGDLHKAQQSLELIQSKI  
VKAAGDTTVIENS DVSPETESSEKETMSVSLNQTVTQLQQLQAVNQQLTKEKEHYQVL  
E

SEQ ID No:175

MGALARALLPLLAQWLLRAAPELAPAPFTLPLRVAAATNRVVAPTPGPGTPAERHADG  
LALALEPALASPAGAAANFLAMVDNLQGD SGRGYYLEMLIGTPPQKLQILVDTGSSNFAV  
AGTPHSYIDTYFDTERSSTYRSKGFDTV KYTQGSWTGFGEDLV TIPKGFNTSFLVNIA  
TIFESENFFLP GIKWNGILGLAYATLAKPSSSLETFFDSLVTQANIPNVFSMQMCGAGLP  
VAGSGTNGGSLVLGGIEPSLYKGDIWYTPIKEEWYYQIEILKLEIGGQSLNLD CREYNAD  
KAIVDSGTTLLRLPQKVFD AVVEAVARASLIPEFSDGFWTGSQ LACWTNSETPWSYFPK  
ISIYLRDENSSRSFRITILPQLYIQPMMGAGLNYECYRFGISPSTNALVIGATVMEGFYVIF  
DRAQKRVGFAASPCA EIAGA AVSEISGPFSTEDVASNCVPAQSLSEPILWIVSYALMSVC  
GAILLV LIVLLLLPFR CQRRPRDPEVVNDESSLVRHRWK

SEQ ID No:176

QNQPYCRGLPDPQDIISQSLQSPSQQA AAKSFYDRISFLIGSDSTHVIPGESPFNKSLASVI  
RGQVLTADGTPLIGVNV SFFHYPEYGYTITRQDGMFDLVANGGASLTLVFERSPFLTQY  
HTVWIPWNV FYVMDTLVMKKEENDIPSCDLSGFVRPNPIIVSSPLSTFFRSPEDSPIPE  
TQVLHEETTIPGTDL KLSYLSSRAAGYKSVLKITMTQSIIPFNL MKVHLMVAVVGRLFQK  
WFPASPNLAYTFIWDKTDAYNQKVYGLSEAVVSVGYEYESCLDLTLWEKRTAILQGYEL  
DASNMGGWTLDKHHVLDVQNGILYKNGENQFISQQPPVVSSIMGNRRRSISCPSCN  
GQADGNKLLAPVALACGIDGSLYVGDFNYVRRIFPSGNVTSVLELRNKDFRHSSNPAHR

YYLATDPVTGDLYVSDTNTRRIYRPKSLTGAKDLTKNAEVVAGTGEQCLPFDEARCGD  
GGKAVEATLMSPKGMMAVDKNGLIYFVDGTMIRKVDQNGIISTLLGSNDLTSARPLTCDTS  
MHISQVRLEWPTDLAINPMDNSIYVLDNNVVLQITENRQVRIAAGRPMHCQVPGVEYPV  
GKHAVQTTLESATAIAVSYSYSGVLYITETDEKKINRIRQVTTDGEISLVAGIPSECDCKNDA  
NCDCYQSGDGYAKDAKLSAPSSLAASPDGTLIADLGNIRIRAVSKNKPLLNSMNFYEV  
ASPTDQELYIFDINGTHQYTVSLVTGDYLYNFSYSNDNDITAVTDSNGNTLRIRDPNRM  
PVRVSPDNQVIWLTIGTNGCLKSMTAQGLELVLFTHGNSGLLATKSDETGWTTFFDY  
DSEGRLTNVTFTPTGVVTNLHGDMDKAITVDIESSSREEDVSITSNLSSIDSFYTMVQDQL  
RNSYQIGYDGLRIIYASGLDSHYQTEPHVLAGTANPTVAKRNMTPGENGQNLVEWR  
FRKEQAQGVNVFGRKLRVNGRNLSSVDFDRTTKTEKIYDDHRKFLLRIAYDTSGHPTL  
WLPSSKLMVNVITYSSTGQIASIQRGTTSEKVDYDGGGRIVSRVFADGKTWSYTYLEK  
SMVLLLHSQRQYIFEYDMWDRLSAITMPSVARHTMQTIRSIGYYRNIYNPPESNASIITDY  
NEEGLLLQTAFLGTSRRVLFKYRRQTRLSEILYDSTRVSFTYDETAGVLKTVNLQSDGFI  
CTIRYRQIGPLIDRQIFRFSEDGMVNARFDYSYDNSFRVTSMQGVINETPLPIDLYQFDDI  
SGKVEQFGKFGVYYDINQIISTAVMTYTKHFDAHGRIKEIQYEIFRSLMYWITIYDNMG  
RVTKREIKIGPFANTTKYAYEYDVDGQLQTVYLNEKIMWRYNYDLNGLHLLNPSNSAR  
LTPLRYDLRDRITRLGDVQYRLDEDGFLRQRGTEIFEYSSKGLLTRVYSKSGSGWTVIYR  
YDGLGRRVSSKTSLGQHLQFFYADLTYPTRITHVYNHSSSEITSLYYDLQGHLFAMEISS  
GDEFYIASDNTGTPLAVFSSNGLMLKQIQYTAYGEIYFDSNIDFQLVIGFHGGLYDPLTKL  
IHFGERDYDILAGRWTTPDIEIWKRIGKDPAPFNLYMFRNNNPASKIHDVKDYITDVNSW  
LVTFGFHLHNAIPGFPVPKFDLTEPSYELVKSQQWDDIPPIFGVQQQVARQAKAFLSLG  
KMAEVQVSRRRAGGAQSWLWFATVKSIGKGVMLAVSQGRVQTNVLNIANEDCIKVAA  
VLNNAFYLENLHFTIEGKDTHYFIKTTTPESDLGTLRLTSGR

SEQ ID No:177

MPVTVTRTTITTTTTSSSGLGSPMIVGSPRALTQPLGLLRLLQLVSTCVAFSLVASVGAW  
TGSMGNWSMFTWCFCFSVTLIILIVELCGLQARFPLSWRNFPITFACYAALFCLSASIIYP  
TTYVQFLSHGRSRDHAIATFFSCIACVAYATEVAWTRARPGEITGYMATVPGLLKVLET  
FVACIIFAFISDPNLYQHQPALWCVAVYAICFILAAIAILLNLGECTNVLPPIFPSFLSGLAL  
LSVLLYATALVLWPLYQFDEKYGGQPRRSRDVSCSRSHAYYVCAWDRRLAVAILTAINL  
LAYVADLVHSAHLVFVKV

SEQ ID No:178

PGGLLLGDVAPNFEANTTVGRIRFHDFLGDSWGILFSHPRDFTPVCTTELGRAAKLAPE  
 FAKRNVKLIALSIDSVEDHLAWSKDINAYNCEEPTTEKLPFPIIDDRNRELAILLGMLDPAEK  
 DEKGMPVTARVVVFVFGPDKKLKSILYPATTGRNFDEILRVVISLQLTAEKRVATPVDWK  
 DGDSVMVLPTIPEEEAKKLFPGVFTKELPSGKKYLRYPQP

SEQ ID No:179

MGTTASTAQQTVSAGTPFEGLQGSGTMDSRHSVSIHSFQSTSLHNSKAKSIIPNKVAPV  
 VITYNCKEEFQIHDELLKAHYTLGRLSDNTPEHYLVQGRYFLVRDVTEKMDVLGTVGSC  
 GAPNFRQVQGGTLVFGMGQPSLSGFRRVLQKLQKDGHRECVIFCVREEPVLFLRADE  
 DFVSYTPRDKQNLHENLQGLGPGVRVESLELAIRKEIHFAQLSENTYHVYHNTEDLWG  
 EPHAVAIHGEDDLHVTEEVYKRPLFLQPTYRYHRLPLPEQGSPLAQDAFVSVLRETP  
 SLLQLRDAHGPPPALVFSCQMVGRTNLGMVLGTLILLHRSGTTSQPEAAPTQAKPLP  
 MEQFQVIQSFLRMVPQGRRMVEEVDRAITACAELHDLKEVVLENQKKLEGIRPESPAQ  
 GSGSRHSVWQRALWSLERYFYLLFNYYLHEQYPLAFALSFSRWLCAHPELYRLPVTLS  
 SAGPVAPRDLIARGSLREDDLVSPDALSTVREMDVANFRRVPRMPIYGTAQPSAKALG  
 SILAYLTDARRLRKVVVWSLREEAVLECDGHTYSLRWPGPPVAPDQLETLEAQLKAHL  
 SEPPPGKEGPLTYRFQTCLTMQEVFSQHRRACPGTYHRIPMPDFCAPREEDFDQLE  
 ALRAALSKDPGTGFVFSCLSGQGRTTAMVVAVLAFWHIQGFPEVGEEELVSVDAKF  
 TKGEFQVVMKVVLQLLPDGHRVKKEVDAALDTVSETMTMPMHYHLREIIICTYRQAKAAKE  
 AQEMRRLQLRSLQYLERYVCLILFNAYLHLEKADSWQRPFSTWMQEVASKAGIYEILNE  
 LGFPELESGEDQPFSLRYRWQEQSCSLEPSAPEDLL

SEQ ID No:180

MAQAKISAKAHEGRFCRSSSMADRSSRLLESLDQLELRVEALRDAATAVEQEKEILLEM  
 HSIQNSQDMRQISDGEREELNLTANRLMGRTLTVEVSVETIRNPQQEESLKHATRIIDEV  
 VSKFLDDLGNKSHLMSLYSACSSEVPPGPVDQKFQSIVIGCALEDQKKIKRRLETLLRN  
 IDNSDKAIKLEHAKGAGSKSLQNTDGKFN

SEQ ID No:181

MRELEAKATKDVERNLSRDLVQEEELMEETEKEKDDKKKKEAAQKKATEQKIKVPEQI  
 KPSVSQPPANSNNGTSTATSTNNNAKRATANNQQPQQQQQQQQPQQQQPQQQPQ  
 PQPQQQQPQQQPQALPRYPREVPPRFRHQEHKQLLKRQGHFPVIAANLGSARKVLNS  
 QSESSALTNQQPQNNGEVQNSKNQSDINHSTSGSHYENSQRGPVSSTSDSSTNCKNA  
 VVSDLSEKEAWPSAPGSDPELASECMDADSASSSESERNITIMASGNTGGEKDGLRNS

TGLGSQNKFFVVGSSSNVGHGSSTGPWGFSHGAIISTCQVSVDAPESKSESSNNRMN  
AWGTVSSSSNGGLNPSTLNSASNHGAWPVLENGLALKGPVGS GSSGINIQ CSTIGQM  
PNNQSINSKVSGGSTHGTWGS LQETCESEVSGTQKVSFSGQPQNITTEMTGPNNTTN  
FMTSSLPNSGSVQNNELPSSNTGAWRVSTMNHPQM QAPSGMNGTSLSHLSNGESKS  
GGSYGTTWGAYGSNYSGDKCSGPNGQANGDTVNATLMQPGVNGPMGTNFQVNTNK  
GGGVWESGAANSQSTSWGSGNGANS GGSRRGWGTPAQNTGTNLPSVEWNKLPSN  
QHSNDSANGNGKTFTNGWKSTEEEDQGSATSQTNEQSSVWAKTGGTVESDGSTEST  
GRLEEKGTGESQSRDRRKIDQHTLLQSIVNRTDLDPRVLSNSGWGQTPIKQNTAWDTE  
TSPRGERKTDNGTEAWGSSATQTFNSGACIDKTSPNGNDTSSVSGWGD PKPALRWG  
DSKGSNCQGGWEDDSAATGMVKSNQWGNCKEEKAAWNDSQKNKQGWGDGQKSS  
QGWSVSASDNWGETSRNNHWGEANKKSSSGGSDSDRSVSGWNE LGKTSSFTWGN  
NINPNNSSGWDESSKPTPSQGWGDPPKSNQSLGWGDSSKPVSSPDWNKQQDIVGS  
WGIPPATGKPPGTGWLGGPIAPAKEEEPTGWEESPESIRRKMEIDDGTSAWGDPSK  
YNYKNVNMWNKNVPNGNSRSDQQAQVHQLLTPASAINKEASSGSGWGEPWGEPT  
PATTVDNGTSAWGKPIDSGPSWGEPIAAASSTSTWGSSSVGPQALSKSGPKSMQDG  
WCGDDMPLPGNRPTGWEEEEEDVEIGMWNSNSSQELNSSLNWPPYTKKMSSKGLSGK  
KRRRERGM MKGNKQEEAWINPFVKQFSNISFSRDSPEENVQSNKMDLSGGMLQDK  
RMEIDKHSLNIGDYNRTVGKGPGRPQISKESMERNPYFDKDGIVADESQNMQFMSS  
QSMKLPPSNSALPNQALGSIAGLGMQNLNSVRQNGNPSMFGVGNTAAQPRGMQQPP  
AQPLSSSQPNLRAQVPPPLLSPQVPVSLKYAPNNGGLNPLFGPQQVAMLNQLSQLNQ  
LSQISQLQRLLAQQQRAQSQRSVPSGNRPQQDQQGRPLSVQQQMMQQSRQLDPNLL  
VKQQTTPSQQQPLHQ PAMKSFLDNVMPHTTPELQKGPSPINAFSNFPIGLNSNLNVNM  
DMNSIKEPQSRLRKWTTVDSISVNTSLDQNSSKHGAISSGFRLEESPFPYDFMNSSTS  
PASPPGSIGDGWPRAKSPNGSSSVNWPPEFRPGEPWKGYPNIDPETDPYVTPGSVIN  
NLSINTVREVDHLRDRNSGSSSSSLNTTLPSTSAWSSIRASNYNVPLSSTAQSTSARNSD  
SKLTWSPGSVTNTSLAHELWKVPLPPKNITAPSRPPPGLTGQKPLSTWDNSPLRIGG  
GWGNSDARYTPGSSWGESSSGRITNWLVLKNLTPQIDGSTLR TCMQHGPLITFHLNL  
PHGNALVRYSSKEEVVKAQKSLHMCVLGNTTILAEFASEEEISRFFAQSQLTPSPGWQ  
SLGSSQSRLGSLDCSHSFSSRTDLNHWNGAGLSGTNCGDLHGTSLWGTPHYSTSLW  
GPPSSSDPRGISSPSPINAFLSVDHLGGGGESM

SEQ ID No:182

MNHQQQQQQQKAGEQQLSEPEDMEMEAGD TDDPPRITQNPVINGNVALSDGHNTAE  
EDMEDDTSWRSEATFQFTVERFSRLSESVLSPPCFVRNLPWKIMVMPRFYPDRPHQK

SVGFFLQCNAESDSTSWSCHAQAVLKIINYRDDEKSFSRRISHLFFHKENDWGFSNFM  
AWSEVTDPEKGFIDDDKVTFEVFVQADAPHGVAWDSKKHTGYVGLKNQGATCYMNSL  
LQTLFFTNQLRKAVYMMPTGDDSSKSVPLALQRVFYELQHSDKPVGTTKLTKSFGWE  
TLDSFMQHDVQELCRVLLDNVENKMKGTCEGTIPKLFRGKMVSIIQCKEVDYRSDRR  
EDYYDIQLSIKGGKNIFESFVDYVAVEQLDGDNKYDAGEHGLQEAEKGVKFLTLPVHLH  
QLMRFMYPQTDQNIKINDRFEFPEQLPLDEFLOKTDPKDPANYILHAVLVHSGDNHGG  
HYVVYLNPKGDGKWCKFDDDVSRCTKEEAIEHNYGGHDDDLVRHCTNAYMLVYIRE  
SKLSEVLQAVTDHDIPQQQLVERLQEEKRIEAQKRKERQEAHLYMQVQIVAEDQFCGHQ  
GNDMYDEEKVKYTVFKVLKNSSLAEFVQSLSQTMGFQDQIRLWPMQARSNGTKRPA  
MLDNEADGNKTMIELSDNENPWTIFLETVDPELAASGATLPKFDKDHDVMLFLKMYDPK  
TRSLNYCGHIYTPISCKIRDLLPVMCDRAGFIQDTSILYEEVKPNLTERIQDYDVS LDKAL  
DELMGDII VFQKDDPENDNSELPTAKE YFRDLYHRVDVIFCDKTIPNDPGFVVTL SNRM  
NYFQVAKTVAQRLNTDPM LLQFFKSQGYRDGPGNPLRHNYEGTLRDLLQFFKPRQPK  
KLYYQQLKMKITDFENRRSFKCIWLNSQFREEEITLYPDKHGCVRDLLEECKKAVELGE  
KASGKLRLL EIVSYKIIGVHQEDELLECLSPATSRTFRIEEIPLDQVDIDKENEMLVTVAHF  
HKEVFGTFGIPFLLRIHQGEHFREVMKRIQSLLDIQEKEFEKFKFAIVMTGRHQYINEDEY  
EVNLKDFEPQPGNMSHPRPWLGLDHFNKAPKRSRYTYLEKAIKIHN

SEQ ID No:183

MATCAEILRSEFPEIDGQVFDYVTGVLHSGSADFESVDDLVEAVGELLQEVS GDSKDDA  
GIRAVCQRM YNTLRLAEPQSQGNSQVLLDAPIQLSKITENYDCGTKLPGLLKREQSSTV  
NAKKLEKAEARLKAKQEKRSKDTLKT SNPLVLEEASASQAGSRKESRLESSGKNKSY  
DVRIENFDVSFGDRVLLAGADVNLAWGRRYGLVGRNGLGKT TLLKMLATRSLRVP AHIS  
LLHVEQE VAGDDTPALQSVLES DSVREDLLRRERELTAQIAAGRAEGSEAAELAEIYAKL  
EEIEADKAPARASVILAGLGFTPKMQQQPTREFSGGWRMRLALARALFARPDLLLLDEP  
TNMLDVRAILWLENYLQTWPSTILVVSHDRNFLNAIATDIIHLHSQRLDGYRGDFETFIKS  
KQERLLNQREYEAQQQYRQHIQVFIDRF RYNANRASQVQSKLMLEKLPELKPVDKE  
SEVVMKFDPDGFEKFSPPIQLDEVDFYYDPKHVIFSRLSVSADLESRICVVGENGAGKST  
MLKLLLGD LAPVRGIRHAHRNLKIGYFSQH HVEQLDLNVS AVELLARKFPGRPEEEYRH  
QLGRYGISGELAMRPLASLGGQKSRVAF AQMTMPCPNFYILDEPTNHLDMETIEALGR  
ALNNFRGGVILVSHDERFIRLVCRELWVCEGGGVTRVEGGFDQYRALLQE QFRREGFL

SEQ ID No:184

MLFWHTQPEHYNQHNHSGSYLRDVLALPIFKQEEPQLSPENEARLPPLQYVLCATSPA  
 VKLHEETLTYNQGGQSYEIRLLENRKLGDQDLNFKYVKSIRVVFHRRRLQYTEHQQLE  
 GWRWSRPGDRILDIDIPLSVGILDPRASPTQLNAVEFLWDPKASAFIQVHCISTEFTP  
 RKHGGGEKGVPPFRVQIDTFKQENGEYTEHLHSASCQIKVFKPKGADRKQKTDREKMEK  
 RTAQEKEKYQPSYETTILTECSPWPDVAYQVNSAPSPSYNGSPNSFGLGEGNASPTHP  
 VEALPVGSDHLLPSASIQDAQWLHRNRFSQFCRLFASFSGADLLKMSRDDLVQICGP  
 ADGIRLFNAIKGRNVRPKMTIYVCQEQNRVPLQKRDGSGDSNLSVYHAIFLEELTTL  
 ELIEKIANLYSISPQHIHRVYRQGPTGIHVVSNMVQNFQDESCFVLSTIKAESNDGYHII  
 LKCGL

SEQ ID No:185

MASVTLSEAELVYVHGVQEDLRVDGRGCEYRCVEVETDVVSNTSGSARVKLGHTDI  
 LVGVKAEMGTPKLEKPNEGYLEFFVDCSASATPEFEGRGDDLGTEIANTLYRIFNNKS  
 SVDLKTLCISPREHCWVLYVDVLLLECGGNLFDASIAVKAALFNTRIPRVRVLEDEEGSK  
 DIELSDDPYDCIRLSVENVPCIVTLCKIGYRHVVDATLQEEACSLASLLSVTSKGVVTCM  
 RKVGKGSOLDPESIFEMMETGKRVGKVLHASLQSVLHKEESLGPKRQKVGFLG

SEQ ID No:186

MAWVLKMDEVIESGLVHDFDASLSGIGQELGAGAYSMSDVLALPIFKQEDSSLPLDGET  
 EHPPFQYVMCAATSPAVKLHDETTLTYLNQGGQSYEIRMLDNRKMGDMPEINGKLKVSIR  
 VVFHRRRLQYTEHQQLEGWKWNRPGDRLLDLIPMSVGIIIDTRTNPSQLNAVEFLWDP  
 AKRTSAFIQVHCISTEFTPRKHGGGEKGVPPFRIQVDTFKQENGEYTDHLHSASCQIKVFK  
 PKGADRKQKTDREKMEKRTAHEKEKYQPSYDTTILTEMRLEPIIEDAVEHEQKKSSKRT  
 LPADYGDLSAKRGSCSPWPDAPTAYVNNSPSPAPTFTSPQQSTCSVPDSNSSSPNHQ  
 GDGASQTSGEQIQPSATIQETQQWLLKNRFSYTRLFSNFSGADLLKLTKEDLVQICGA  
 ADGIRLYNSLKSRSVRPRLTIYVCREQPSSTVLQGGQQAASSASENGSGAPYVYHAIYL  
 EEMIASEVARKLALVFNIPLHQINQVYRQGPTGIHILVSDQMVQNFQDESCFLFSTVKA  
 SSDGIHILK

SEQ ID No:187

MAWALKLPLADEVIESGLVQDFDASLSGIGQELGAGAYSMSDVLALPIFKQEESLPPD  
 NENKILPFQYVLCATSPAVKLHDETTLTYLNQGGQSYEIRMLDNRKLGELPEINGKLKVSIF  
 RVVFHRRRLQYTEHQQLEGWRWNRPGDRILDIDIPMSVGIIIDPRANPTQLNTVEFLWDP  
 AKRTSVFIQVHCISTEFTMRKHGGGEKGVPPFRVQIDTFKENENGEYTEHLHSASCQIKVFK

PKGADRKQKTDREKMEKRTPHEKEKYQPSYETTLTECSPWPEITYVNNSPSPGFNSS  
HSSFSLGEGNGSPNHQPEPPPVTDNLLPTTTTQEAQQWLHRNRFFSTFTRLFTNFSGA  
DLLKLTRDDVIQICGPADGIRLFNALKGRMVRPRLTIYVCQESLQLREQQQQQQQQQQK  
HEDGDSNGTFFVYHAIYLEELTAVELTEKIAQLFSISPCQISQIYKQGPTGIHVLISDEMIQ  
NFQEEACFILD TMKQETNDSYHIILK

SEQ ID No:188

MSTPPLAASGMAPGPFAGPQAQQAAREVNTASLCRIGQETVQDIVYRTMEIFQLLRNM  
QLPNGVTYHTGTYQDRLTKLQDNLRQLSVLFRKLRLVYDKCNENCGGMDPIPVEQLIPY  
VEEDGSKNDDRAGPPRFASEERREIAEVNKKLKQKNQQLKQIMDQLRNLIWDINAMLA  
MRN

SEQ ID No:189

MAQKMDCGAGLLGFQAEASVEDSALLMQTLMEAIQISEAPPTNQATAAASPQSSQPPT  
ANEMADIQVSAAAARPKSAFKVQNATTKGPNGVYDFSQAHNAKDVNPNTQPKAAFKSQ  
NATSKGPNAAYDFSQAATTGELAANKSEMAFKAQNATTKVGP NATYNFSQSLNANDLA  
NSRPKTPFKAWNDTTKAPTADTQTQNVNQAKMATSQADIETDPGISEPDGATAQTSAD  
GSQAQNLESRTIIRGKRTRKINN LNVEENSSGDQRRAPLAAGTWRSAPVPVTTQNPPG  
APPNVLWQTPLAWQNP SGWQNQTARQTTPPARQSPPARQTTPPAWQNP VAWQNPVIW  
PNPVIWQNPVIWPNPIVWPGPVVWP NPLAWQNPPGWQTTPPGWQTTPPGWQGPPDWQ  
GPPDWPLPPDWPLPPDWPLPTDWPLPPDWIPADWPIPPDWQNL RPSPNL RPSPNSRA  
SQNP GAAQPRDVALLQERANKLVKYLMLKDYTKVPIKRSEMLRDIIREYTDVYPEIIERA  
CFVLEKKFGIQLKEIDKEEHLYILISTPESLAGILGTTKDTPKLGLLLVILGVIFMNGNRASE  
AVLWEALRKMGLRPGVRHPLLGD LRKLLTYEFVKQKYLDYRRVPNSNPPEYEFLWGLR  
SYHETSKMKVLR FIAEVQKRDP RDWTAQFMEAADEALDALDAAA EAEARAEARTRM  
GIGDEAVSGPWSWDDIEFELLTWDEEGDFGDPWSRIPFTFWARYHQNARS RFPQTFA  
GPIIGPGGTASANFAANFGAIGFFWVE

SEQ ID No:190

RRRLDADPAAGRRAPAPKRLSVPDAPRPTPTMKRASAGGSRL LAWVLWLQAWQVAA  
PCPGACVCYNEPKVTTSCPQQGLQAVPVGIPAASQRIFLHG NRISHVPAASFRACRNLT  
ILWLHSNVLARIDAA AFTGLALLEQLDLSDNAQLRSVDPATFHGLGRLHTLHLDRCGLQE  
LGPGLFRGLAALQYLYLQDNALQALPDDTFRDLGNLTHLFLHG NRISSVPERAFRGLHS  
LDRLLLHQNRVAHVH PHAFRDLGRLMTLYLFANNLSALPTEALAPLRALQYLRLNDNPW

VCD CRARPLWAWLQKFRGSSSEVPCSLPQRLAGRDLKRLAANDLQGCAVATGPYHPI  
WTGRATDEEPLGLPKCCQPDAAADKASVLEPGRPASAGNALKGRVPPGDSPPGNGSG  
PRHINDSPFGTLPGSAEPPLTAVRPEGSEPPGFPTSGPRRRPGCSRKNRTRSHCRLGQ  
AGSGGGGTGDSESGALPSLTCSLTPLGLALVLWTVLGPC

SEQ ID No:191

MAEQEPTAEQLAQIAAENEDEHSVNYKPPAQKSIQEIQELDKDDESLRKYKEALLGRV  
AVSADPNVNPVVVTGLTLVCSSAPGPLELDLTGDLESFKKQSFVLKEGVEYRIKISFRVN  
REIVSGMKYIQHTYRKGVKIDKTDYMGVSGYPRAEEYEFLTPVEEAPKGMLARGSYSIK  
SRFTDDDKTDHLSWEWNLTIKKDWKD

SEQ ID No:192

MAKHEQILVLDPPPTDLKFKGPFTDVVTTNLKLRNPSPDRKVCVKVKTAPRRYCVRPNSG  
IIDPGSTVTVSVMLQPFDPNEKSKHKFMVQTIFAPPNTSDMEAVWKEAKPDELMSK  
LRCVFEMPENENDKLNDEPSKAVPLNASKQDGPMPKPHSVSLNDTETRKLMEECKRL  
QGEMMKLSEENRHLRDEGLRLRKVAHSDKPGSTSTASFRDNVTSPLPSLLVVIAAIFIGF  
FLGKFIL

SEQ ID No:193

MGAGATGRAMDGPRLLLLLLLGVSLGGAKEACPTGLYTHSGECCKACNLGEGVAQPC  
GANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEADDAVCRCAYGYY  
QDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDEANHVDPCLPCTVCE  
DTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAG  
VTTVMGSSQPVVTRGTTDNLIPVYCSILAAVVVGLVAYIAFKRWNSCKQNKQGANSRP  
VNQTPPPEGEKLSHSDSGISVDSQSLHDQQPHTQTASGQALKGDGGLYSSLPPAKREEV  
EKLNGSAGDTWRHLAGELGYQPEHIDSFTHEACPVRALLASWATQDSATLDALLAAL  
RRIQRADLVESLCSESTATSPV

SEQ ID No:194

MAQRKNAKSSGNSSSSSGSGSGSTSAGSSSPGARRETKHGGHKNGRKGGLSGTSFFT  
WFMVIALLGWVTSVAVVWFDLVDYEEVLGKLGIYDADGDGDFDVEDDAKVLLGLKERST  
SEPAVPPEEAEPHTEPEEQVPVEAEPQNIIDEAKEQIQSLLHEMVHAEHVEGEDLQQE  
DGPTGEPQQEDDEFLMATDVDDRFELEPEVSHEETESYHVEETVSQDCNQDMEEM  
MSEQENPDSSEPVEDERLHHD TDVTYQVYEEQAVYEPLENEGIEITEVTAPPEDNPV



EDSQVIVEEVSIFPVEEQQEVPPETNRKTDDPEQKAKVKKKKPKLLNKFDKTIKAELDAA  
EKLRKRGKIEEAVNAFKELVRKYPQSPRARYGKAQCEDDLAEKRRSNEVLRGAIETYQE  
VASLPDVPADLLKLSLKRRSDRQQFLGHMRGSLTLQRLVQLFPNDTSLKNDLGVGYLL  
IGDNDNAKKVYEEVLSVTPNDGFAKVHYGFILKAQNKIAESIPYLKEGIESGDPGTDDGR  
FYFHLGDAMQRVGNKEAYKWYELGHKRGHFASVWQRSLINVNGLKAQPCGPKETGYT  
QLVKSLEARNWKLIRDEGLAVMDKAKGLFLPEDENLREKGDWSQFTLWQQGRRNENAC  
KGAPKTCTLLEKFPETTGCRRGQIKYSIMHPGTHVWPHTGPTNCRLRMHLGLVIPKEGC  
KIRCANETKTWEEGKVLIFDDSFHEVWQDASSFRLIFVDVWHPELTPQQRRSLPAI

SEQ ID No:195

KMATPLAVNSAASLWGPYKDIWHKVGNALWRRQPEAVHLLDKILKKHKPDFISL FKNPP  
KNVQQHEKVQKASTEGVAIQGQQGTRLLPEQLIKEAFILSDLFDIGELAAVELLLAGEHQ  
QPHFPGLTRGLVAVLLYWDGKRCIANSLKALIQSRRGKTWLELSPELASMTTRFTDEL  
MEQGLTYKVLTLVSQIDVNNEFEKLQRERGLGSEKHRKEVSDLIKECRQSLAESLFAWA  
CQSPLGKEDTLLIGHLERVTVEANGSLDAVNALLMALLYCFDISFIEQSTEERDDMIHQ  
LPLLTEKQYIATIHSLRLQDSQLWKLPGLQATVRLAWALALRGISQLPDVTALAEFTEADE  
AMAE LAIADNVFLFLMESVVVSEYFYQEEFYIRRVHNLITDFLALMPMKVKQLRNRADED  
ARMIHMSMQMGNEPPISLRRDLEHMLLIGELYKKNPFHLELALEYWCPTPLQTPTIM  
GSYLGVAHQRPQRQVVL SKFVRQMGDLLPPTIYIPYKMLQGLANGPQCAHYCFSL  
KVNGSSHVENIQGAGGSPVSWEHFFHSLMLYHEHLRKDLPSADSVQYRHLPSRGITQK  
EQDGLIAFLQLTSTIITWSENARLALCEHPQWTPVVILGLLQCSIPPVLKAELLKTAAFG  
KSPEIAASLWQSLEYTQILQTVRIPSQRQAIGIEVELNEIESRCEEYPLTRAFCQLISTLVE  
SSFPSNLGAGLRPPGFDPYLQFLRDSVFLRFRTRAYRRAAEKWEVAEVLLEV FYKLLR  
DYEPQLED FVDQFVELQGEEIAYKPPGFSLMYHLLNESPMLELALS LLEEGVKQLDTYA  
PFPGKKHLEKAVQHCLALLNLTLQKENLFMDLLRESQLALIVCPLEQLLQGINPRTKKAD  
NVVNIARYLYHGNTNPELAFESAKILCCISCNSNIQIKLVGDFTHDQSSISQKLMAGFVECL  
DCEDAE EFVRLEEGSELEKKLVAIRHETRIHILNLLITSLECNPPNLALYLLGFELKKPVST  
TNLQDPGVLGCPRTCLHAILNILEKGTEGRTGPVAVRESPQLAELCYQVIYQLCACSDTS  
GPTMRYLRTSQDFLFSQLQYLPFSNKEYEISMLNQMSWLMKTASIELRVTSLNRQRSHT  
QRLLHLLLDMPVKPYSDGEGGIEDENRSVSGFLHFDTATKVR RKILNILDSIDFSQEIPE  
PLQLDFFDRAQIEQVIANCEHKNLRGQTV CNVKLLHRVLVAEVNALQGMAAIGQRPLLM  
EEISTVLQYVVGRNKLLQCLHAKRHALESWRQLVEIILTACPQDLIQAEDRQLIIRDILQDV  
HDKILDDEAAQELMPVVAGAVFTLTAHLSQAVLTEQKQTSVLGP AEAHYAFMLDSCFTS  
PPPEENPLVG FASIGDSSLYIILKKLLDFILKTGGGFQVRVTHLYGSLLY LQIAQRPDEP

DTLEAAKKT MWERLTAPEDVFSKLQRENIAIESYGAALMEVVCRDACDGHEIGRMLAL  
 ALLDRIVSV DKQQQWLLYLSNSGYLKVLVDSLVEDDRTLQSL LTPQPPLLKALYTYESK  
 MAFLTRVAKIQQGALELLRSGVIVRLAQCQVYDMRPETDPQSMFGMRDPPMFIPTPVD  
 RYRQILLPALQLCQVILTSSMAQHLQAAGQVLQFLISHSDTIQAILRCQDVSAGSLQELAL  
 LTGIISKAALPGILSELVDVDVNEGSLMELQGHIGRFQRQCLGLLSRFSGSDRLRQFKFQD  
 DNVEGDKVSKKDEIELAMQQICANVMEYCQSLMLQSSPTFQHAVCLFTPSLSETVNRD  
 GPRQDTQAPVVPYWRLPGLGIIIYLLKQSANDFFSYD SHRQSVSKLQNV EQLPPDEIK  
 ELCQSVMPAGVDKISTAQKYVLARRRLVKVINNRALLSLCSFIIETCLFILWRHLEYLL  
 HCMPTDSQDSL FASRTLFKSRRLQDSFASETNLDFRSGLAIVSQHDL DQLQADAINAFG  
 ESLQKKLLDIEGLYSKVR SRYSF IQALVRRIRGLLRISRN

SEQ ID No:196

MSFLKSFP PP GPAEGLLRQQPDTEAVLNGKGLGTGTLYIAESRLSWLDGSGLGFSLEY  
 PTISLHALSRDRSDCLGEHLYVMVNAKFEEESKEPVADEEEEDSDDDVEPITEFRFVPS  
 DKSALEAMFTAMCECQALHPDPEDEDSDDYDGE EYDVEAHEQGQGDIP TFYTYEEGL  
 SHLTAEGQATLERLEGMLSQSVSSQYNMAGVRTEDSIRDYEDGMEVDTTPTVAGQFE  
 DADV DH

SEQ ID No:197

HNAASPGGARGHRVPLTEACKDSRIGGMMKTL L LFVGLLLTWESGQVLGDQTVSDNEL  
 QEMSNQGSKYVNKEIQNAVNGVKQIKTLIEKTNEERKTLLSNLEEAKKKKEDALNETRE  
 SETKLKELPGVCNETMMALWEECKPCKLQTCMKFYARVCRSGSLVGRQLEEF LNQS  
 SPFYFWMNGDRIDS LLENDRQQTHMLDVMQDHFSRASSIIDELFQDRFFTREPQD TYH  
 YLPFSLPHRRPHFFFPKSRIVRSLMPFSPYEPLNFHAMFQPFLEMIHEAQQAMDIHFHS  
 PAFQHPPTEFIREGDDDR TVCREIRHNSTGCLRMKDQCDKCREILSVDCSTNNPSQAK  
 LRRELD ESLQVAERLTRKYNELLKSYQWKMLNTSSLLEQLNEQFNWVSRLANLTQGED  
 QYYLRVTTVASHTSDSDVPSGVTEVVVKLFDSDPITVTVPVEVSRKNPKFMETVAEKAL  
 QEYRK KHREE

SEQ ID No:198

EKSGGPGTREREREKREERQSAWGRKERGREGWVRRRERSAANPRRRRAWSPSQNS  
 SPSRSRSQGGGCRDRQPCMMHLRLFCILLAAVSGAEGWGYYGCDEELVGPLYARSLG  
 ASSYYSLLTAPRFARLHGISGWSPRIGDPNPWLQIDLMKKHRIRAVATQGSFNSWDWV  
 TRYMLLYGDRVDSWTPFYQRGHNSTFFGNVNESAVVRHDLHFHFTARYIRIVPLAWN P

RGKIGLRLGLYGCPYKADILYFDGDDAISYRFPRGVSRSLWDVFAFSFKTEEKDGLLLHA  
EGAQGDYVTLELEGAHLLLHMSLGSSPIQPRPGHTTVSAGGVLNDQHWYVRVDRFG  
RDVNFTLDGYVQRFILNGDFERLNLDTMFIGGLVGAARKNLAYRHNFRGCIENVIFNRV  
NIADLAVRRHSRITFEGKVAFRCLDPVPHPINFGGPHNFVQVPGFPRRGRLAVSFRFRT  
WDLTGLLLSRLGDGLGHVELTSEGQVNVSIAQSGRKKLQFAAGYRLNDGFWHEVNF  
VAQENHAVISIDDVEGAEVRVSYPLLIRTGTSYFFGGCPKPASRWDCHSNQTAFHGCM  
ELLKVDGQLVNLTLVEGRRLGFYAEVLFDTCGITDRCSNMCEHDGRCYQSWDDFICY  
CELTGYKGETCHTPLYKESCEAYRLSGKTSGNFTIDPDGSGPLKPFVVYCDIRENRAWT  
VVRHDRLWTTTRVTGSSMERPFLLGAIQYWNASWEEVSALANASQHCEQWIEFSCYNSR  
LLNTAGGYPYSFWIGRNEEQHFYWGGSQPGIQRACGLDRSCVDPALYCNCADADQPQ  
WRTDKGLLTFVDHLPVTQVVIGDTNRSTSEAQFFLRPLRCYGDRNSWNTISFHTGAALR  
FPPIRANHSLDVSFYFRTSAPSGVFLENMGGPYCQWRRPYVRVELNTSRDVVFAFDVG  
NGDENLTVHSDDFEFNDDEWHLVRAEINVKQARLRVDHRPWVLRPMPLQTYIWMEYD  
QPLYVGS AELKRRPFVGC LRAMRLNGVTLNLEGRANASEGTSPNCTGHCAHPRLPCF  
HGGRCVERYSYTCDCLTAFDGPYCNHDIGGFFEPGTWMRYNLQSALRSAAREFSH  
MLSRPVPGYEPGYIPGYDTPGYVPGYHGPYRLPDYPRPGRPVPGYRGPVYNVTGEE  
VSFSFSTSSAPAVLLYVSSFVRDYMAVLIKDDGTLQLRYQLGTSPYVYQLTTRPVTGQ  
PHSINITRVYRNLFIQVDYFPLTEQKFSLLVDSQLDSPKALYLGRVMETGVIDPEIQRYNT  
PGFSGCLSGVRFNNVAPLKTHFRTPRPM TAEALRVQGELSESNCGAMPRLVSEVP  
PELDPWYLPPDFPYHDEGWVAILLGLFLVAFLLGLVGM LVLFLYLNHRYKGSYHTNEP  
KAAHEYHPGSKPPLPTSGPAQVPTPTAAPNQAPASAPAPAPTAPAPGPRDQNL PQIL  
EESRSE

SEQ ID No:199

MASRLLRGAGTLAAQALRARGPSGAAAMRSMASGGGVPTDEEQATGLEREIMLAACK  
GLDPYNVLAPKGASGTREDPNLVPSISNKRIVGCICEEDNTSVVFWLHKGEAQRCP  
CGAHYKLVPQQLAH

SEQ ID No:200

MAEDMETKIKNYKTAPFDSRFPNQNQTRNCWQNYLDFHRCQKAMTAKGGDISVCEWY  
QRVYQSLCPTSWVTDWDEQRAEGTFPGKI

SEQ ID No:201

MAPEVLPKPRMRGLLARRLRNHMAVAFVLSLGVAALYKFRVADQRKKAYADFYRNYDV  
MKDFEEMRKAGIFQSVK

SEQ ID No:202

MAGLQLMTPASSPMGPFFGLPWQQEAIHDNIYTPRKYQVELLEAALDHNTIVCLNTGSG  
KTFIAVLLTKELSYQIRGDFSRNGKRTVFLVNSANQVAQQVSAVRTHSDLKVGEYSNLE  
VNASWTKERWNQEFTKHQVLIMTCYVALNVLKNGYLSLSDINLLVFDECHLAILDHPYR  
EIMKLCENCPSCPRI LGLTASILNGKCDPEELEEKI QKLEKILKSNAETATDLVVLD RYTS  
QPCEIVVDCGPFTDRSGLYERLLMELEEALNFINDCNISVHSKERDSTLISKQILSDCRAV  
LVVLGPWCADKVAGMMVRELQKYIKHEQEELHRKFLLFTDTFLRKIHALCEEHFSPASL  
DLKFVTPKVIKLEILRKYKPYERQQFESVEWYNNRNQDNYVSWSDSEDDDEDEEIEEK  
EKPETNFPSPFTNILCGIIFVERRYTAVVLNRLIKEAGKQDPELAYISSNFITGHGIGKNQP  
RNKQMEAEFRKQEEVLRKFRAHETNLLIATSIVEEGVDIPKCNLVVRFDLPT EYRSYVQS  
KGRARAPISNYIMLADTDKIKSFEEDLKTYKAIEKILRNKCSKSVDTGETDIDPVMDDDDV  
FPPYVLRPDDGGPRVTINTAIGHINRYCARLPSPDPTH LAPKCRTR ELPDGT FYSTLYLPI  
NSPLRASIVGPPMSCVRLAERVVALICCEKLHKIGELDDHLM PVGKETVKYEEELDLHDE  
EETSVPGRPGSTKRRQCYPKAIPECLRDSYPRPDQPCYLYVIGMVLTTPLPDELNFRRR  
KLYPPEDTTRCFGILTAKPIPIPHFPVYTRSGEVTISIELKKSGFMLS LQMLELITRLHQYI  
FSHILRLEKPALEFKPTDADSAYCVLPLNVVNDSSSTLDIDFKFMEDIEKSEARIGIPSTKYT  
KETPFVFKLEDYQDAVIIPRYRNFDQPHRFYVADVYTDLTPLSKFPSPEYETFAEYYKTK  
YNLDLTNLNQPLLDVDHTSSRLNLLTPRHLNQKGKALPLSSAEKRKAKWESLQNKQILV  
PELCAIHPIPASLWRKAVCLPSILYRLHCLLTAEELRAQTASDAGVGVRSLPADFRYPNL  
DFGWKKSIDSKSFISISNSSSAENDNYCKHSTIVPENAAHQGANRTSSLENHDQMSVNC  
RTLLSESPGKLHVEVSADLTAINGLSYNQNLANGSYDLANRDFCQGNQLNYYKQEIPVQ  
PTTSYSIQNLYSYENQPQPSDECTLLSNKYLDGNANKSTSDGSPVMAVMPGTTDTIQVL  
KGRMDSEQSPSIGYSSRTLGPNPGLILQALTLNASDGFNLERLEMLGDSFLKHAITTYL  
FCTYPDAHEGRLSYMRSSKVSNCNLYRLGKKKGLPSRMVVSIFDPPVNWLP PGYVVN  
QDKSNTDKWEKDEMTKDCMLANGKLDEDEYEEDEEEESLMWRAPKEEADYEDDFLE  
YDQEHIRFIDNMLMGSGAFVKKISLSPFSTTDSAYEWKMPKKSSLGSM PFSSDFEDFDY  
SSWDAMCYLDPSKAVEEDDFVVGFWNPSEENC GVD TGKQSISYDLHTEQCIADKSIAD  
CVEALLGCYLTSCGERAAQLFLCSLGLKVLPIKRTDREKALCPTRENFNSQQKNLSVS  
CAAASVASSRSSVLKDSEYGCLKIPPRCMFDHPDADKTLNHLISGFENFEKKINYRFKNK  
AYLLQAFTHASYHYNTITDCYQRLEFLGDAILDY LITKHLYEDPRQHSPGVLTDLRSALVN  
NTIFASLAVKYDYHKYFKAVSPELFHVIDDFVQFQLEKNEMQGM DSELRRSEED EEEKEE

DIEVPKAMGDIFESLAGAIYMDSGMSLETVWQVYYPMRPLIEKFSANVPRSPVRELLE  
MEPETAKFSPAERTYDGKVRVTVEVVGKKGKFKGVGRSYRIAKSAAARRALRSLKANQP  
QVPNS

SEQ ID No:203

MRLLAGWLCLSLASVWLARRMWTLRSPLTRSLYVNMTSGPGGPAAAAGGRKENHQW  
YVCNREKLCESLQAVFVQSYLDQGTQIFLNNSIEKSGWLFIQLYHSFVSSVFSLFMSRTS  
INGLLGRGSMFVFSPDQFQRLKINPDWKTHRLLDLGAGDGEVTKIMSPHFEEIYATELS  
ETMIWQLQKKKYRVLGINEWQNTGFQYDVISCLNLLDRCDQPLTLLKDIRSVLEPTRGR  
VILALVLPFHPYVENVGKWEKPSEILEIKGQNWEEQVNSLPEVFRKAGFVIEAFTRLPY  
LCEGDMYNDYYVLDDAVFVLKPV

SEQ ID No:204

PPRASFAAAVAAAARDSRRRAVMADPAAPTPAAPAPAQAPAPAPEAVPAPAAAPVPAPA  
PASDSASGPSSDFGPEAGSQRLLFSHDLVSGRYRGSVHFGLVRLIHGEDSDSEGE EEG  
RGSSGCSEAGGAGHEEGRASPLRRGYVRVQWYPEGVKQHVKETKLKLED RSVVPRD  
VVRHMRSTDSQCGTVIDVNIDCAVKLIGNCIIPVNSKDLQHIWPFMYGDYIAYDCWL G  
KVYDLKNQIILKLSNGARCSMNTE DGAKLYDVCPHVSDSGLFFDDSYGFYPGQVLIGPA  
KIFSSVQWLSGVKPV LSTKSKFRVVVEEVQVVELKVTWITKSFCPPGGTDSVSPPPSVIT  
QENLGRVKRLGCFDHAQRQLGERCLYVFPKVEPAKIAWECPEKNCAQGEGSMAKKV  
KRLLKKQVVRIMSCSPDTQCSR DHSMEDPDKKGESKTKSEAESASPEETPDGSASPVE  
MQDEGAEEPHEAGEQLPPFLLKEGRDDRLHSAEQDADDEAADD TDDTSSVTSSASST  
TSSQSGSGTSRKKSIPLSIKNLKRKHKRKKNKITRDFKPGDRVAVEVTTMTSADVMWQ  
DGSVECNIRSNDLFPVHLDNNEFCPGDFVVDKRVQSCPDPAVYGVVQSGDHIGRTC  
MVKWFKLRPSGDDVELIGEEEDVSVYDIADHPDFRFRRTT DIVIRIGNTEDGAPHKEDEPS  
VGQVARVDVSSKVEVWADNSKTIILPQHLYNIESEIEESDYDSVEGSTSGASSDEWED  
DSDSWETDNGLVEDEHPKIEEPPIPPLEQPVAPEDKGVVISEEAATAAVQGAVAMAAPM  
AGLMEKAGKDGP PKSFRELKEAIKILESLKNMTVEQLLTGSPTSPTVEPEKPTREKKFLD  
DIKKLQENLKKTLDNVAIVEEEKMEAVPDVERKEDKPEGQSPVKA EWPSETPVLCQQC  
GGKPGVTFTSAKGEVFSVLEFAPSNHSFKKIEFQPPEAKKFFSTVRKEMALLATSLPEGI  
MVKTFEDRMDLFSALIKGPTRTPYEDGLYLFDIQLPNIYPAVPPHFCYLSQCSGRLNPNL  
YDNGKVCV SLLGTWIGKGTERWTSKSSLLQVLISIQGLILVNEPY YNEAGFDSDRGLQE  
GYENSR CYNEMALIRVVQSMTQLVRRPPEVFEQEIRQHFSTGGWRLVNRIESWLETHA  
LLEKAQALPNGVPKASSSPEPPAVAELSDSGQQEPEDGGPAPGEASQGS DSEGGAQS

LASASRDHTDQTSETAPDASVPPSVKPKKRRKSYRSFLPEKSGYPDIGFPLFPLSKGFIK  
SIRGVLTQFRAALLEAGMPECTEDK

SEQ ID No:205

MPGSAAKGSEL SERIESFVETLKRGGGPRSSEEMARETLGLLRQIITDHRWSNAGELM  
ELIRREGRRMTAAQPSETTVGNMVRRLKIIREEYGR LHGRSDESDQQESLHKLLTSGG  
LNEDFSFHYAQLQSNII EAINELLVELEGT MENIAAQALEHIHSNEVIMTIGFSRTVEAFLK  
EAARKRK FHVIVAECAPFCQGH EMAVNLSKAGIETTVMTDAAIFAVMSRVN KVIIGTKTIL  
ANGALRAVTGTH TLALAAKHSTPLIVCAPMFKLSPQFPNEEDSFHKFVAPEEVLPFTE  
GDILEKVS VHCPVFDYVPPELITLFISNIGGNAPSYIYRLMSELYHPDDHVL

SEQ ID No:206

MRCCHICKLPGRVMGIRVLRLSLVILVLLL VAGALTALLPSVKEDKMLMLRREIKSQGK  
STMDSFTLIMQTYNRTDLLL KLLNH YQAVPNLHKVIVVWNNIG EKAPDELWNSLGPHPIP  
VIFKQQTANRMRNRLQVFPELETNAVLMVDDDTLISTPDLVFAFSVWQQFPDQIVGFVP  
RKHVSTSSGIYSYGSFEMQAPGSGNGDQYSMV LIGASFFNSKYLELFQRQPAAVHALID  
DTQNCDDIAMNFIIAKHIGKTSGIFVKPVNMDNLEKETNSGYSGMWHRAEHALQRSYCI  
NKLVNIYDSMPLRYSNIMISQFGFPYANYKRKI

SEQ ID No:207

MAVAVAVAARRRRSWASLVLAFLGVCLGITLAVDRSNFKTCEESSFCKRQRSIRPGLSP  
YRALLDSLQLGPD SLTVHLIHEVTKVLLVLELQGLQKNMTRFRIDELEPRRPRYRVPDVL  
VADPPIARLSVSGRDENSVELTMAEGPYKIILTARPFRLDLLED RSLLLSVNARGLLEFEH  
QRAPRVSFSDKVNLT LGSIWDKIKNLF SRQGSKDPAEGDGAQPEETPRDGDKEETQG  
KAEKDEPGAW EETFKTHSDSKPYGPMSVGLDFSLPGMEHVYGIPEHADNLR LKVTEG  
GEPYRLYNLDVFQYELYNPMALYGSVPVLLAHNPHRDLGIFWL NAAETWVDISSNTAGK  
TLFGKMMDYLQGSGETPQTDVRWMSETGIIDVFLLLGPSISDVFRQYASLTGTQALPPL  
FSLGYHQSRWNYRDEADVLEVDQGFDHNLPCDVIWLDIEHADGKRYFTWDPSRFPQ  
PRTMLERLASKRRKLVAIVDPHIKVDSGYRVHEELRNLGLYVKTRDGS DYEGWCWPGS  
AGYPDFTNPTMRAWWANMFSYDNYEGSAPNLFVWNDMNEPSVFNGPEVTMLKDAQH  
YGGWEHRDVHNIYGLYVHMATADGLRQRSGGMERPFV LARAFFAGSQRFGAVWTGD  
NTAEWDHLKISIPMCLSLGLVGLSFCGADVGGFFKNPEPELLVRWYQMGAYQPFFRAH  
AHLDTGRREPWLLPSQHNDIIRDALGQRYSLLPFWYTLLYQAHREGIPVMRPLWVQYP  
QDVTTFNIDDQYLLGDALLVHPVSDSGAHGVQVYLP GQGEVWYDIQSYQKHHGPQTLY

LPVTLSSIPVFQRRGGTIVPRWMRVRRSSECMKDDPITLFVALSPQGTAAQGELFLDDGHT  
FNYQTRQEFLRRFSFSGNTLVSSSADPEGHFETPIWIERVVIIGAGKPAAVVLQTKGSP  
ESRLSFQHDPETSVLVLRKPGINVASDWSIHLR

SEQ ID No:208

MKLKLVFLAYFLVSIAGLLYALVQLGQPCDCLPPLRAAAEQLRQKDLRISQLQAEARR  
PPPAPAPPEPEALPTIYVVTPTYARLVQKAELVRLSQTLSLVPRLHWLLVEDAEGPTPL  
VSGLLAASGLLFTHLVVLTPKAQRLREGEPGWVHPRGVEQRNKALDWLRGRGGAVGG  
EKDPPPPGTQGVVYFADDDNTYSRELSEEMRWTRGVSVWPVGLVGGLRFEGPQVQD  
GRVVGFTAWEPSRPFPPVDMAGFAVALPLLLDKPNAQFDSTAPRGHLESSLLSHLVDP  
KDLEPRAANCTRVLVWHTRTEKPKMKQEEQLQRQGRGSDPAIEV

SEQ ID No:209

MTTVVVHVDSKAELTTLLEQWEKEHGGSGQDMVPILTRMSQLIEKETEEYRKGDPPDFD  
DRHPGRADPECMLGHLLRILFKNDDFMNALVNAYVMTSREPPLNTAACRLLLDIMPGL  
TAVVFQEKEGIVENLFKWAREADQPLRTYSTGLLGAMENQDIAANYRDENSQLVAIVL  
RRLRELQLQEVALRQENKRPSRKLSSPEPLPLDEEAVDMDYGDMAVDVVDGDQEEA  
SGDMEISFHLD SGHKTSSRVNSTTKPEDGGLKKNKSAKQGDRENFRKAKQKLGFS  
SSDPDRMFVELSNSSWSEMSPWVIGTNYTLYPMTPAIEQRILQYLTPLGEYQELLPIFMQLG  
SRELMMFYIDLKQTN DVLLTFEALKVKFLKILGHRGFFKNFVFFNLRWSTLSPRLECSG  
AILAHCNLRLLGSSDSPASASRVCMHPHNVLSDVVNYTLWLMECSHASGCCHATMFFS  
ICFSFRAVLELFD RYDGLRRLVNLVSTLEILNLEDQGALLSDDEIFASRQTGKHTCMALR  
KYFEAHLAIKLEQVKQSLQRTEGGILVHPQPPYKACSYTHEQIVEMMEFLIEYGPAQLY  
WEPAEVFLKLSCVQLLLQLISACNWKTYARNDTVRFALDVLAILTVVPKIQQLAESVD  
VLDEAGSTVSTVGISIILGVAEGEFFIHDAEIQKSALQIIINCVCGPDNRISIGKFISGTPRR  
KLPQNPKSSEHTLAKMWNVQSNNGIKVLLSLLSIKMPITDADQIRALACKALVGLSRSS  
TVRQIISKLP LFSSCQIQQLMKEPVLQDKRSDHVKFCKYAAELIERVSGKPLLIGTDVSLA  
RLQKADVVAQSRISFPEKELLLLIRNHLISKGLGETATVLTKEADLPMTAASHSSAFTPVT  
AAASPVSLPRTPRIANGIATRLGSHAAVGASAPSAPTAHPQPRPPQGPLALPGPSYAGN  
SPLIGRISFIRERPSPCNGRKIRVLRQKSDHGAYSQSPAIAKKQLDRHLPSPPTLDSIITEYL  
REQHARCKNPVATCPPFSLFTPHQCPEPKQRRQAPINFTSRLNRRASF PKYGGVDGG  
CFDRHLIFSRFRPISVFREANEDESFTCCAFSARERFLMLGTCTGQLKLYNVFSGQEE  
ASYNCHNSAITHLEPSRDGSLLLTSATWSQPLSALWGMKSVFDMKHSFTEDHYVEFSK  
HSQDRVIGTKGDIAHIYDIQTGNKLLTLFNPDLANNYKRNCATFNPTDDLVLNDGVLWDV

RSAQAIHKFDKFNMNISGVFHPNGLEVIINTEIWDLRTFHLLHTVPALDQCRVVFNHTGT  
 VMYGAMLQADDEDDLMEERMKSPFGSSFRFTFNATDYKPIATIDVKRNIFDLCTDTKDCY  
 LAVIENQGSMDALNMDTVCRLYEVGRQRLAEDEDEEEEDQEEEEQEEEDDDDEDDDDTD  
 DLDELDTDQLLEAELEEDDNENAGEDGDNDFSPSDEELANLLEEGEDGEDEDSDADE  
 EVELILGDTDSSDNSDLEDDIILSLNE

SEQ ID No:210

MASCPDSDNSWVLAGESESLPVETLGPASRMDPESERALQAPHSPSKTDGKELAGTMD  
 GEGTLFQTESPQSGSILTEETEVEKGTLEGDVCGVEPPGPGD TVVQGD LQETT VVTGLG  
 PDTQDLEGQSPQSLPSTPKAAWIREEGRCSSSDDDDTDVDMEGLRRRRRGREAGPPQP  
 MVPLAVENQAGGEGAGGELGISLNMCLLGALVLLGLGVLLFSGGLSESETGPMEEVER  
 QVLPDPEVLEAVGDRQDGLREQLQAPVPPDSVPSLQNMGLLLDKLAKENQDIRLLQAAQ  
 LQAQKEELQSLMHQPKGLEEENALRGALQQGEAFQRALESELQQLRARLQGLEADC  
 VRGPDGVCLSGGRGPQGDKAIREQGPREQEPELSFLKQKEQLEAEAQALRQELERQR  
 RLLGSVQQDLERSLQDASRGDPAHAGLAELGHR LAQKLQGLENWGQDPGV SANASKA  
 WHQKSHFQNSREWSGKEKWWDGQRDRKAEHWKHKKEESGRERKKNWGGQEDRE  
 PAGRWKEGRPRVEESGSKKEGKRQGPKEPPRKSGSFHSSGEKQKQPRWREGTKDS  
 HDPLPSWAELLRPKYRAPQGCSGVDECARQEGLTFFGT ELAPVRQQELASLLRTYLAR  
 LPWAGQLTKELPLSPAFFGEDGIFRHDRLRFRDFVDALEDSLEEVAVQQTGDDDEVDD  
 FEDFIFSHFFGDKALKKRSGKKDKHSQSPRAAGPREGHSHSHHHHHHRG

SEQ ID No:211

AVPGADHGRQPAGNRRSIFSRTDLVRAGVLKEKPLWFDVYDAFPPLREP VFQRPRVR  
 YGKAKAPIQDIWYHEDRIRAKFYSVYGSGQRAFDLFNPNFKSTCQRFVEKYTELQKLGE  
 TDEEKLFVETGKALLAEGVILRRVGEQGLNTEVVTFFGNPNT

SEQ ID No:212

MRTL FNLLWLALACSPVHTTLSKSDAKKAASKTLEKSQFSDKPVQDRGLVVTDLKAES  
 VVLEHRSYCSAKARDRH FAGDVLGYVTPWNSHGYDVTKVFGSKFTQISPVWLQLKRR  
 GREMFEVTGLHDVDQGWMRAVRKHAKGLHIVPRLLFEDWTYDDFRNVLDSEDEIEELS  
 KTVVQVAKNQHFDFGVVEVWNQLLSQKRVGLIHMLTHLAEALHQARLLALLVIPPAITPG  
 TDQLGMFTHKEFEQLAPVLDGFSLMTYDYSTA HQPGPNAPLSWVRACVQVLDPKSKW  
 RSKILLGLNFYGM DYATSKDAREPVVGARYIQTLKDHRPRMVWDSQASEHFFEYKKS  
 SGRHVVFYPTLKS LQVRLELARELGVGVS IWELGQGLDYFYDLL



SEQ ID No:213

MWIMTRTWGGQARVNGKIKAPARAGRTVSSCIFSSCLWFLPFRSSCLKTQPDSDACQP  
ASPTRAAALPTRMGGTTPPRCPRAERSRGSTGIARASALAAGGAGVLRGRDQSAIRAA  
TPDLGRQLSSHCDGHWGAPSILVKFSL

SEQ ID No:214

LPSGLHFSFSSLKVISGQKLTRLFTSNQILTSECLSCVELLEDPNISASLILSIIGLLSQLAV  
DIETRDCLQNTYNLNSVLAVVCRSSHTDSVFLQCIQLLQKLTYNVKIFYSGANIDELITF  
LIDHIQSSSEDELKMPCLGLLANLCRHNLSVQTHIKTLSNVKSFYRTLITLLAHSSLTVVVFAL  
LSILSSLTLNEEVGEKLFHARNIHQTFQLIFNILINGDGTLTRKYSVDLLMDLLKNPKIADYL  
TRYEHFSSCLHQVLGLLNGKDPDSSSKVLELLLAFCSVTQLRHMLTQMMFEQSPPGSA  
TLGSHTKCLEPTVALLRWLSQPLDGSENCVLALELFKEIFEDVIDAANCSSADRFVTL  
LPTILDQLQFTEQNLDEALTRKKCERIAKAIEVLLTLCGDDTLKMHIKILTTVKCTTLIEQQ  
FTYGKIDLGFGTKVADSELCKLAADVILKTLDLINKLKPLVPGMEVSFYKILQDPRLITPLA  
FALTSDNREQVQSGRLILLEAAPLPDFPALVLGESIAANNAYRQQETEHIPRKMPWQSS  
NHSFPTSICKLTPHLKDGVPGLNIEELIEKLQSGMVVKDQICDVRISDIMDVYEMKLSTLA  
SKESRLQDLLETKALALAQADRLIAQHRCQRTQAETEARTLASMLREVERKNEELSVLL  
KAQQVESERAQSDIEHLFQHNRKLESVAEEHEILTKSYMELLQRNESTEKKNKDLQITC  
DSLNKQIETVKKLNESLKEQNEKSIAQLIEKEEQRKEVQNQLVDREHKLNLHQKTKVQ  
EEKIKTLQKEREDKEETIDILRKELSRTEQIRKELSIKASSLEVQKAQLEGRLEEKESLVKL  
QQEELNKHSHMIAMIHSLSGGKINPETVNLSI

SEQ ID No:215

MPAYALLGEFTQAKVIINDTEDEPTLEFDKKIYWVNESAGFLFAPIERKGDASSIVSAICY  
TVPKSAMGSSLYALESGSDFKSRGMSAASRVIFGPGVTMSTCDVMLIDDSEYEEEQFR  
VYLGLPLGNHWSGARIGKNNMATITISNDEDAPTIEFEEAAYQVREPAGPDAIAILNIKVIR  
RGDQNRSTSKVRCSTRDGSAAQSGVDYYPKSRVLKFSPGVDHIFKVEILSNEDREWHES  
FSLVLGPDDPVEAVLGDVTTATVTILDQEAAGSLILPAPPVIVTLADYDHVEEVTKEGVKK  
SPSPGYPLVCVTPCDPHFPRYAVMKERCSEAGINQTSVQFSWEVAAPTGDNGARSPF  
ETITDNTPTFTSVNHMVLDISIYFSRRFHVRCVAKAVDKVGHVGTPLRSNIVTIGTDSAICHT  
PVVAGTSRGFQAQSFIA TLKYLDVKHKEHPNRSRGRWCPLPHID

SEQ ID No:216

RVYADAPAKLLLPPPAAWDLAVRLRGAEAAASERQVYSVTMKLLLLHPAFQSCLLLTLLG  
 LWRTTPEAHASSLGAPAIASAASFLQDLIHRYGEGDSLTLQQLKALLNHLDVGVGRGNVT  
 QHVQGHRLNLSTCFSSGDLFTAHNFSEQSRIGSSELQEFCTILQQLD SRACTSENQEN  
 EENEQTEEGRPSSAVEVWGYGLLCVTVISLCSLLGASVVPFMKKTFFYKRLLLYFIALAIGTL  
 YSNALFQLIPEAFGFNPLEDYYVSKSAVVFGGFYLFFFTEKILKILLKQKNEHHHGHSHYA  
 SESLPSKKDQEEGVMEKLQNGDLDHMIPQHCSSELDGKAPMVDEKVIVGSLSVQDLQA  
 SQSACYWLKGVRYSDIGTLAWMITLSDGLHNFIDGLAIGASFTVSVFQGISTSVAILCEEF  
 PHELGD FVILLNAGMSIQQALFFNFLSACCCYLG LAFGILAGSHFSANWIFALAGGMFLYI  
 SLADMFP EMNEVCQEDERKGSILIPFIIQNLGLLTGFTIMVVLTMYSGQIQIG

SEQ ID No:217

MPAYALLGEFTQAKVIINDTEDEPTLEFDKKIYWVNESAGFLFAPIERKGDASSIVSAICY  
 TVPKSAMGSSLYALESGSDFKSRGMSAASRVIFGPGVTMSTCDVMLIDDSEYEEEQFR  
 VYLGLPLGNHWSGARIGKNNMATITISNDEDAPTIEFEEAAYQVREPAGPDAIAILNIKVIR  
 RGDQNR TSKVRCSTRDGS AQSGVDYYPKSRVLKFSPGVDHIFFKVEILSNEDREWHES  
 FSLVLGPDDPVEAVLGDVTTATVTILDQEAAGSLILPAPPVVTLADYDHVEEVTKEGVKK  
 SPSPGYPLVCVTPCDPHFPRYAVMKERCSEAGINQTSVQFSWEVAAPTDGNGARSPF  
 ETITDNTPTFTSVNHMVLDSIYFSRRFHVRCVAKAVDKVGHVGTPLRSNIVTIGTDSAICHT  
 PVVAGTSRGFQAQSFIA TLKYLDVKHKEHPNRIHISVQIPHQDGMLPLISTMPLHNLHFL  
 SESIYRHQHVC SNLVT TYDLRGISEAGFLDDVVDSTALGPGYDRPFQFDPSVREP KTI  
 QLYKHLNLKSCVWTFDAYYDMTELIDVCGGSVTADFQVRDSAQSFLT VHVPLYVSYIYV  
 TAPRGWASLEHHTEMEFSFFYDTVLWRTGIQTDSVLSARLQIIRIYIREDGRLVIEFKTHA  
 KFRGQFVMEHHTLPEVKSFVLTPDHLGGIEFDLQLLWSAQTFDSPHQLWRATSSYNRK  
 DYSGEYTIYLIPCTVQPTQPWVDPGEKPLACTAHAPERFLIPIAFQQTNRPVVPVYSLNT  
 EFQLCNNEKVFLMDPNTSDMSLAEMDYKGAFSKGQILYGRVLWNPEQNLNSAYKLQLE  
 KVYLCTGKDGYPFFDPTGTIYNEG PQYGCIPNKHLKHRFLLDRNQPEVTDKYFHDV  
 PFEAHFASELPDFHVVS NM PGVDGFTLKV DALYKVEAGHQWYLQVIYIIGPDTISGPRV  
 QRSLTAPLRRNRRLVEPDGQLILDDSLIYDNEGDQVKNGTNMKSLNLEMQELAVAASL  
 SQTGASIGSALAAIMLLLLVFLVACFINRK CQKQRKKKPAEDILEEYPLNTKVEVPKRHPD  
 RVEKNVNRHYCTVRNVN ILSEPEAA YTFKGAKVKRLNLEVRVHNNLQDGTEV

SEQ ID No:218

MGAAAGRSPHLGPAPARRPQRSLLLLQLLLLVAAPGSTQAQAAPFPELCSYTWEAVDT  
 KNNVLYKINICGSVDIVQCGPSSAVCMHDLKTRTYHSVGDSVLR SATRSLLFNTTVSC

DQQGTNHRVQSSIAFLCGKTLGTPEFVTATECVHYFEWRTTAACKKDIFKANKEVPCYV  
 FDEELRKHDLNPLIKLSGAYLVDDSDPDTSLFINVCRDIDTLRDPGSQLRACPPGTAACL  
 VRGHQAFDVGQPRDGLKLVRKDRLVLSYVREEAGKLDFCDGHSPA VTITFVCP SERRE  
 GTIPKLTAKSNCRYEIEWITEYACHRDYLESKTC SLSGEQQDV SIDLTPLAQSGGSSYIS  
 DGKEYLFYLNVCGETEIQFCNKKQAAVCQVKKSDTSQVKAAGRYHNQTLRYSDGDLTLI  
 YFGGDECSSGFQRM SVINFECNKTAGNDGKGTPVFTGEVDCTYFFTWDTEYACVKEK  
 EDLLCGATDGKKRYDLSALVRHAEPEQNWEAVDGSQTETEEKHFFINICHRVLQEGKA  
 RGCPEDAAVCAVDKNGSKNLGKFISPMKEKGNIQLSYSDGDDCGHGGKKIKTNITLVCK  
 PGDLESAPVLR TSGEGGCFYEF EWRTAAACVLSKTEGENCTVFDSQAGFSFDLSPLTK  
 KNGAYKVETKKYDFYINVC GPVSVSPCQPD SGACQVAKSDEKTWNLGLSNAKLSYYD  
 GMIQLNYRGGTPYNNERHTPRATLITFLCDRDAGVGFPEYQEEDNSTYNFRWYTSYAC  
 PEEPLECVVTD PSTLEQYDLSSLAKSEGGLG GNWYAMDNSGEHVTWRKYIINVCRPL  
 NPVPGCNRYASACQMKYEKDQGSFTEVVSISNLGMAKTGPVVEDSGSLLLEYVNGSA  
 CTTSDGRQTTYTTRIHLVCSRGR LNSHPIFSLNWECVVSFLWNTEAACPIQTTTDDTQQA  
 CSIRDPNSGFVFNLNPLNSSQGYNVSGIGKIFMFNVCGTMPVCGTILGKPASGCEAETQ  
 TEELKNWKPARPVGIEKSLQLSTEGFITLYKGPLSAKGTADAFIVRFVCNDDVYSGPLK  
 FLHQDIDSGQGIRNTYFETALACVPSPVDCQVTDLAGNEYDLTGLSTVRKPWTAVDT  
 SVDGRKRTFYLSVCNPLPYIPGCQGS AVGSCLVSEGN SWNLGVVQMSPQAAANGSLSI  
 MYVNGDKCGNQRFSTRITFECAQISGSPAFQLQDGCEYVFIWRTVEACPVRVEGDNC  
 EVKDPRHGNLYDLKPLGLNDTIVSAGEYTY YFRVCGKLSSDVCPTSDKSKVVSSCQEK  
 REPQGFHKVAGLLTQKLTYENGLLKMNFTGGDTCHKVYQRSTAIFFYCDRGTQRPVFL  
 KETSDCSYLF EWRTQYACPPFDLTECSFKDGAGNSFDLSSLSRYSDNWEAITGTGDPE  
 HYLINVCKSLAPQAGTEPCPPEAAACLLGGSKPVNLGRVRDGPQWRDGIIVLK YVDGDL  
 CPDGIRKKSTTIRFTCSSESQVNSRPMFISAVEDCEYTFAWPTATACPMKSNEHDDCQVT  
 NPSTGHLFDLSSLSGRAGFTAAYSEKGLVYMSICGENENCPPGVGACFGQTRISVGKA  
 NKRLRYVDQVLQLVYKDGSPCPSKSGLSYKSVISFVCRPEAGPTNRPM LISLDKQTCTL  
 FFSWHTPLACEQATECSVRNGSSIVDLSPLIHRTGGYEAYDESEDDASDTNPDFYINIC  
 QPLNPMHAVPCPAGAAVCKVPIDGPPIDIGRVAGPPILNPIANEIYLN FESSTPCLADKHF  
 NYTSLIAFHCKRGVSMGTPKLLRTSECDFFEWETPVVCPDEV RMDGCTLTDEQLLYS  
 FNLSSLSTSTFKVTRDSRTYSVGVCTFAVGPEQGGCKDGGVCLLSG TKGASFGRLQS  
 MKLDYRHQDEAVVLSYVNGDRCP PETDDGVPCVFPFIFNGKSYEECIIESRAKLWCSTT  
 ADYDRDHEWGF CRHSNSYRTSSII FKCEDEDEDIGRPQVFSEVRGCDVTFEWKTKVVC  
 PKKLECKFVQKHKTYDLRLSSLTG SWSLVHNGVSYIINLCQKIYKGPLGC SERASICR  
 RTTTGDVQVLGLVHTQKLGVIGDKVVVTYSKGYPCGGNKTASSVIELTCTKT VGRPAFK

RFDIDSCTYYFSWDSRAACAVKPQEVQMVNGTITNPINGKSFSLGDIYFKLFRASGDMR  
TNGDNYLYEIQLSSTSSRNPACSGANICQVKPNDQHFSTRKVGTSKTKYYLQDGDLDV  
VFASSSKCGKDKTKSVSSTIFFHCDPLVEDGIPEFSHETADCQYLFSWYTSAVCPLGVG  
FDSENPGDDGQMHKGLSERSQAVGAVLSLLLVALTCCLLALLYKKERRETVISKLTTC  
CRRSSNVSYKYSKVNKEEETDENETEWLMEEIQLPPPRQGKEGQENGHITTKSVKALS  
SLHGDDQDSEDEVLTIPVVKVHSGRGAGAESSHPVRNAQSNALQEREDDRVGLVRGE  
KARKGKSSSAQQKTVSSTKLVSFHDDSDDLLHI

SEQ ID No:219

MAFPFRRRLRLGPRGLPLLLSGLLLPLCRAFNLVDVSPAKEYSGPEGSYFGFAVDFFVPS  
ASSRMFLLVGAPKANTTQPGIVEGGQVLKCDWSSTRRCQPIEFDATGNRDYAKDDPLE  
FKSHQWFGASVRSKQDKILACAPLYHWRTMKQEREPVGTCFLQDGTCTVEYAPCRS  
QDIDADGQGFCQGGFSIDFTKADRVLLGGPGSFYWQQQLISDQVAEIVSKYDPNVYSIK  
YNNQLATRTAQAFDDSYLGYSVAVGDFNGDGIDDFVSGVPRAARTLGMVYIYDGKNM  
SSLYNFTGEQMAAYFGFSVAATDINGDDYADVFIGAPLFMDRGS DGKLQEVGQVSVSL  
QRASGDFQTTKLNGFEVFARFGSAIAPLGDLDDQDGFNDIAIAAPYGGEDKKGIVYIFNGR  
STGLNAVPSQILEGQWAARSMPPSFGYSMKGATDIDKNGYPDLIVGAFGVDRAILYRAR  
PVITVNAGLEVYPSILNQDNKTCSLPGTALKVSCFNVRFLKADGKGVLPKLNQFQVELL  
LDKLGKQGAIRRALFLYSRSPSHSKNMTISRGGMLMQCEELIAYLRDESEFRDKLTPTIFM  
EYRLDYRTAADTTGLQPILNQFTPANISRQAHILLDCGEDNVCKPKLEVSVSDQKKIYIG  
DDNPLTLIVKAQNQGEGAYEALIVSIPLQADFIGVVRNNEALARLSCAFKTENQTRQVV  
CDLGNPMKAGTQLLAGLRFVHQQSEMDTSVKFDLQIQSSNLFDKVSPVVS HKVDLAV  
LAAVEIRGVSSPDHIFLPIPNWEHKENPETEEDVGPVVQHIYELRNNGPSSFSKAMLHLQ  
WPYKYNNNTLLYILHYDIDGPMNCTSDMEINPLRIKISSLOTTEKNDTVAGQGERDHLITK  
RDLALSEGDIHTLGCGVAQCLKIVCQVGRLD RGKSAILYVKSLLWTETFMNKENQNHSY  
SLKSSASFNVIEFPYKNLPEDITNSTLVTTNVTWGIQAPMPVPVWVILAVLAGLLLLAV  
LVFVMYRMGFFKRVRPPQEEQEREQLQPHENGEGNSET

SEQ ID No:220

MTEKMSSFLYIGDIVSLYAEGSVNGFISTLGLVDDRCVVHPEAGDLANPPKKFRDCLFKV  
CPMNRYS AQKQYWKAKQAKQGNHTEAALLKKLQHAAELEQKQNESENKKLLGEIVKY  
SNVIQLLHIKSNKYLTVNKRLPALLEKNAMRVSLDAAGNEGSWFYIHPFWKLRSEGDNIV  
VGDKVVLMPVNAGQPLHASNIELLDNPGCKEVNAVNCNTSWKITLFMKYSSYREDVLK  
GGDVVRLFHAEQEKFLTCDYEKKQHIFLRTTLRQSATSATSSKALWEIEVVHHDPCRG

GAGQWNSLFRFKHLATGNYLAAELNPDYRDAQNEGKNVRDGPPTS KKKRQAGEKIM  
 YTLVSVPHGNDIASL FELDATT LQRADCLVPRNSYVRLRHLC TNTWVTSTSIPI DTDEER  
 PVMLKIGTCQTKEDKEAFAIVSVPLSEVRDLDFANDANKVLATT VKKLENGTITQNERRF  
 VTKLLEDLIFFVADV PNNGQEVLDVVITKPNRERQKLMREQNILAQVFGILKAPFKEKAG  
 EGSMLRLEDLGDQRYAPYKYMLRLCYRVL RHSSQQDYRKNQEYIAKNFCVMQSQIGYDI  
 LAEDTITPLLHNNRKLLEKHITAKEIETFVSLLRRNREPRFLDYLS DLCVSNNTTAIPVTQELI  
 CKFMLSPGNADILIQTKVVS MQADNPMESSILSDDIDDEE VWLYWIDSNKEPHGKAIRHL  
 AQEAKEG TKADLEVLTYYRYQLNLFARMCLDRQYLAINQISTQLSVDLILRCVSDES LPF  
 DLRASFCRLMLMHVDRDPQESVVPVRYARLWTEIPTKITIHEYDSITDSSRNDMKRKF  
 ALTMEFVEEYLKEVVNQPFPGDKEKNKLTFEVVHLARNLIYFGFYSFSELLRLTRTLLAI  
 LDIVQAPMSSYFERLSKFQDGGNNVMRTIHGVGEMMTQMVLSRGSIFPMSVPDVPPSI  
 HPSKQGSPTHEHEDVTVM DTKLKIIELQFILSVRLDYRISYMLS IYKKEFGEDNDNAETSA  
 SGSPDTLLPSAIVPDIDEIAAQAETMFAGRKEKNPVQLDDEGGRTFLRVLIHLMHDYAPL  
 LSGALQLLFKHFSQRAEVLQAFKQVQLLSNQDVDNYKQIKADLDQLRLTVEKSELWVE  
 KSSNYENGEIGESQVKGGEEPIEESNILSPVQDGTKKPQIDSNKSNKYRIVKEILIRLSKL  
 CVQNKKCRNQHQRL LKNMGAHSVVDLLQIPYEKNDEKMNEVMNLAHTFLQNFCRGN  
 PQNQVLLHKHLNLFLTPGLLEAETMRHIFMNNYHLCNEISERVVQHFVHCIETHGRHVE  
 YLRFQTIVKADGKYVKKCQDMVMTELINGGEDVLIFYNDRASFPILLHMMC SERDRGD  
 ESGPLAYHITLVELLA ACTEGKNVYTEIKCNSLLPLDDIVRVVTHDDCIPEVKIAYVNFVNH  
 CYVDTEVEMKEIYTSNHIWKL FENFLVDMARVCNTTTDRKHADIFLEKCVTESIMNIVSG  
 FFNSPFS DNSTSLQTHQPVFIQLLQSAFRIYNCTWPNPAQKASVESCIRTLAEVAKNRGI  
 AIPVDLDSQVNTLFMKSHSNMVQRAAMGWRLSARSGPRFKEALGGPAWDYRNII EK LQ  
 DVVASLEHQFSPMMQAEFSVLVDVLYSPELLFPEGSDARIRCGAFMSKLINHTKKLMEK  
 EEKLCIKILQTLREM LEKKDSFVEEGNTLRKILLNRYFKGDYSIGVNGHLSGAYS KTAQV  
 GGSFSGQDSDKMGISMSDIQCLLDKEGASELVIDVIVNTKNDRIFSEGIFLGIALLEG GNT  
 QTQYSFYQQLHEQKKSEKFFKVLYDRMKA AQKEIRSTVTVTNTIDLGNKKRDDD NELMT  
 SGPRMRVRDSTLHLKEGMKGQLTEASSATSKAYCVYRREMDPEIDIMCTGPEAGNTEE  
 KSAEEVTMSPAIAIMQPILRFLQLLCENHNRELQNFLRNQNNKTNYNLVCETLQFLDCIC  
 GSTTGGLGLLGLYINEKNVALVNQNLES LTEYCQGPCHENQTCIATHESNGIDIIIALILND  
 INPLGKYRMDLV LQLKNNASKLLLAIMESRHDSENAERILFNM RPRELVDVMKNAYNQG  
 LECDHGDDEGGDDGVSPKDVGHNIYILAHQLARHNKLLQQMLKPGSDPDEGDEALKYY  
 ANHTAQIEIVRHDRTMEQIVFPVPNICEYLTRESKCRVFNTTERDEQGSKVNDFFQQTE  
 DLYNEMKWQKKIRNNPALFWFSRHISLWGSISFNLAVFINLAVALFY PF GDDGDEGTLS  
 PLFSVLLWIAVAICTSMLFFF SKPVGIRPFLVSIMLRSIY TIGLGPTLILLGAANLCNKIVFLV

SFVGNRGTFTRGYRAVILDMAFLYHVAYVLVCMGLFVHEFFYSFLLFDLVYREETLLNV  
IKSVTRNGRSIILTAVLALILVYLFSIIGFLFLKDDFTMEVDRLKNRTPVTGSHQVPTMTLTT  
MMEACAKENCSTIPASNTADEEYEDGIERTCDTLLMCIVTVLNQGLRNGGGVGDVLR  
RPSKDEPLFAARVVYDLLFYFIVIIVLNLIFGVIIIDTFADLRSEKQKKEEILKTTFCICGLER  
DKFDNKTVSFEEHIKSEHNMWHYLYFIVLVKVKDPTEYTGPESYVAQMIVEKNLDWFPR  
MRAMSLVSNEGDSEQNEIRSLQEKLESTMSLVKQLSGQLAELKEQMTEQRKNKQRLG  
FLGSNTPHVNHHMPPH

SEQ ID No:221

MVSSGCRMRLWFIIVISFLPNTEGFSRAALPFGLVRRELSCEGYSIDLRCPGSDVIMIES  
ANYGRDDDKICDADPFQMENTDCYLPDAFKIMTQRCNNRTQCIVVTGSDVFPDPCPGT  
YKYLEVQYECVPYIFVCPGTLKAIVDSPCIYEAQKAGAWCKDPLQAADKIYFMPWTPY  
RTDTLIEYASLEDFQNSRQTTTYKLPNRVDGTGFVVYDGAVFFNKERTRNIVKFDLRTRI  
KSGEAIINYANYHDTSPYRWGGKTDIDLAVDENGWLWVIYATEQNNGMIVISQLNPYTLRF  
EATWETVYDKRAASNAFMICGVLYVRSVYQDNESETGKNSIDYIYNTRLNRGEYVDVP  
FPNQYQYIAAVDYNPRDNQLYVWNNNFILRYSLEFGPPDPAQVPTTAVTITSSAELFKTII  
STTSTTSQKGPMSTTVAGSQEGSKGTKPPPAVSTTKIPPITNIFPLPERFCEALDSKGIK  
WPQTQRGMMVERPCPKGTRGTASYLCMISTGTWNPKGPDLSNCTSHWVNQLAQKIR  
SGENAASLANELAKHTKGPVFAGDVSSSVRLMEQLVDILDAQLQELKPSEKDSAGRSY  
NKAIVDTVDNLLRPEALESWKHMNSSEQAHTATMLLDTLEEGAFVLADNLLPEPTRVSMP  
TENIVLEVAVLSTEGQIQDFKFPLGIKGAGSSIQLSANTVKQNSRNLAKLVFIYRSLGQ  
FLSTENATIKLGADFIGRNSTIAVNSHVISVSINKESSRVYLTDPVLFTLPHIDPDNYFNAN  
CSFWNYSERTMMGYWSTQGCKLVDNKTTRTTCACSHLTNFAILMAHREIAYKDGVEL  
LLTVITWVGIVISLVCLAICIFTFCFFRGLQSDRNTIHKNLCLNLFIAEFIFLIGIDKTKYAIACP  
IFAGLLHFFFLAAFAWMCLEGVQLYLMLVEVFESSEYSRKKYYYVAGYLPATVVGVSAAI  
DYKSYGTEKACWLHVDNYFIWSFIGPVTFIILLNIIFLVITLCKMVKHSNTLKPDSRLENIK  
SWVLGAFALLCLLGLTWSFGLLFINEETIVMAYLFTIFNAFQGVFIFHICALQKKVRKEY  
GKCFRHSYCCGGLPTESPHSSVKASTTRTSARYSSGTQSRIRRMWNDTVRKQSESSFI  
SGDINSTSTLNQGHSLNNARDTSAMDTLPLNGNFNNSYSLHKGDYNDVSVQVDCGLSL  
NDTAFEKMIISELVHNNLRGSSKTHNLELTLPVKPVIGGSSSEDDAIVADASSLMHSDNP  
GLELHHKELEAPLIPQRTHSLLYQPQKKVKSEGTDSYVSQLTAEADHLQSPNRDSLYT  
SMPNLRDSPYPESSPDMEEDLSPSRRENEEDIYYKSMPNLGAGHQLQMCYQISRGNS  
DGYIIPINKEGCIPEGDVREGQMQLVTSL

SEQ ID No:222

MRLTRCQAALAAAITLNLLVLFYVSWLQHQPRNSRARGPRRASAAGPRVTVLVREFEA  
FDNAVPELVDSFLQQDPAQPVVVAADTLPPYPLALPRIPNVRLALLQPALDRPAAASRP  
ETYVATEFVALVPDGARAEAPGLLERMVEALRAGSARLVAAPVATANPARCLALNVSLR  
EWTARYGAAPAAPRCDALDGDVLLRARDLFNLSAPLARPVGTSLFLQTALRGWAVQ  
LLDLTFAAARQPPLATAHARWKAEREGRARRAALLRALGIRLVSWEGGRLEWFGCNKE  
TTRCFGTVVGDTPAYLYEERWTPPCCLRALRETARYVVGVLAAAGVRYWLEGGSSLLGA  
ARHGDIIPWDYDVDLGIYLEDVGNCEQLRGAEAGSVVDERGFVWEKAVEGDFFRVQYS  
ESNHLHVDLWPFYPRNGVMTKDTWLDHRQDVEFPEHFLQPLVPLPFAGFVAQAPNNY  
RRFLELKFGPGVIENPQYPNPALLSLTGSG

SEQ ID No:223

MPRGQKSKLRAREKRQRTRGQTQDLKVGQPTAAEKEESPSSSSSVLRDTASSSLAFGI  
PQEPQREPPTTSAAAAMSCTGSDKGDESQDEENASSSQASTSTERSLKDSLTRKTKM  
LVQFLLYKYMKEPTTKAEMLKIIISKKYKEHFPEIFRKVSQRTELVFGLALKEVNPTTHSY  
ILVSM LGPN DGNQSSAWTLPRNGLLMPLLSVIFLNGNCAREEEIWEFLNMLGIYDGKRH  
LIFGEPRKLITQDLVQEKYLEYQQVPNSDPPRYQFLWGPRAHAETSKMKVLEFLAKVND  
TTPNNFPLLYEEALRDEEERAGARPRVAARRGTTAMTSAYS RATSSSSSQPM

SEQ ID No:224

MTLIEGVGDEVTVLFSVLACLLVLALAWVSTHTAEGGDPLPQPSGTPTPSQPSAAMAAT  
DSMRGEAPGAETPSLRHRGQAAQPEPSTGFTATPPAPDSPQEPLVRLKFLNDSEQVA  
RAWPHDTIGSLKRTQFPGREQQVRLIYQGQLLGDDTQTLGSLHLPNCVLHCHVSTRV  
GPPNPPCPPGSEPGPSGLEIGSLLLPLLLLLLLLLLWYCQIQYRPFPLTATLGLAGFTLLL  
SLLAFAMYRP

SEQ ID No:225

MVVALRYVWPLLLCSPCLLIQIPEEYEGHHVMEPPVITEQSPRRLVVFP TDDISLKCEAS  
GKPEVQFRWTRDGVHFKPKEELGVTVYQSPHSGSFTITGNNSNFAQRFGGIYRCFASN  
KLGTAMSHEIRLMAEGAPKWPKETVKPVEVEEGESVVLPCNPPPSAEPLRIYWMNSKIL  
HIKQDERVTMGQNGNLYFANVLTSDNHSDYICHAHFPGTRTIIQKEPIDLRVKATNSMID  
RKPRLLFPTNSSSHLVALQGQPLVLECIAEGFPTPTIKWLRPSGPM PADRVTYQNHNKT  
LQLLKVGEEDDGEYRCLAENSLGSARHAYYVTEAAPYWLHKPQSHLYGPGETARLDC  
QVQGRPQPEVTWRINGIPVEELAKDQKYRIQRGALILSNVQPSDTMVTQCEARNRHGL

LLANAYIYVVQLPAKILTADNQTYMAVQGSTAYLLCKAFGAPVPSVQWLDEDGTTVLQD  
 ERFFPYANGTLGIRDLQANDTGRYFCLAANDQNNVTIMANLKVKDATQITQGPRSTIEKK  
 GSRVTFTCQASFDPSLQPSITWRGDGRDLQELGSDSKYFIEDGRLVIHSLDYSQDQNY  
 SCVASTELDVVESRAQLLVVGSPGPVPRVLVSLDLHLLTQSQVRVSWSPAEDHNAPIEKY  
 DIEFEDKEMAPEKWYSLGKVPGNQSTSTTLKLSPYVHYTFRVTAINKYGPGEPSPVSETV  
 VTPEAAPEKPNPVDVKGEGETTNMVTWKPLRWMDWNAPQVQYRVQWRPQGTRGP  
 WQEQIVSDPFLVVSNTSTFVPYEIKVQAVNSQGKGPEPQVTIGYSGEDYPQAIPELEGIE  
 ILNSSAVLVKWRPVDLAQVKGHLRGYNVTYWREGSQRKHSKRHIHKDHVVVPANTTSV  
 ILSGLRPYSSYHLEVQAFNGRSGSPASEFTFSTPEGVPGHPEALHLECQSNTSLLLRLW  
 QPPLSHNGVLTGYVLSYHPLDEGGKGQLSFNLDPPELRTHNLTDLSPHLRYRFQLQAT  
 TKEGPGEAIVREGGTMALSGISDFGNISATAGENYSVSWVPKEGQCNFRFHILFKALG  
 EEKGGASLSPQYVSYNQSSYTQWDLQPDTDYEIHLFKERMFRHQMAVKTNGTGRVRL  
 PPAGFATEGWFIGFVSAILLLLVLILCFIKRSKGGKYSVKDKEDTQVDSEARPMKDETF  
 GEYRSLESDNEEKAFGSSQPSLNGDIKPLGSDDSLADYGGSDVDVQFNEGDSFIGQYSG  
 KKEKEAAGGNDSSGATSPINPAVALE

SEQ ID No:226

MAVAVRTLQEQLEKAKESLKNVDENIRKLTGRDPNDVRPIQARLLALSGPGGGGRGRGS  
 LLLRRGFSDSGGGPPAKQRDLEGAVSRLGGERRTRRESRQESDPEDDDVKKPALQSS  
 VVATSKERTRRDLIQDQNMDEKGKQRNRRIFGLLMGTLQKFKQESTVATERQKRRQEI  
 EQKLEVQAEERKQVENERRELFEERRAKQTELRLLEQKVELAQLQEEWNEHNAKIIKY  
 IRTKTKPHLFYIPGRMCPATQKLIIESQRKMNALFEGRRIEFAEQINKMEARPRRQSMKE  
 KEHQVVRNEEQKAEQEEGKVAQREEELEETGNQHNDVEIEEAGEEEEEKEIAIVHSDAE  
 KEQEEEEQKQEMEVMKEEETEVRSEKQQDSQPEEVMDEVENVKHVIADQEVME  
 TNRVESVEPSENEASKELEPEMEFEIEPDKECKSLSPGKENVSALDMEKESEEKEEKES  
 EPQPEPVAQPQPQSQPQLQLQSQSQPVLQSQPPSQPEDLSLAVLQPTPQVTQEQQHL  
 LPERKDFPVESVKLTEVPVEPVLTVHPESKSKTKTRSRSRGRARNKTSKSRSRSSSSSS  
 SSSSSTSSSSSGSSSSSGSSSSSRSSSSSSSSSTSGSSGRDSSSSTSSSSSESRSRSGRG  
 HNRDRKHRRSVDRKRRDTSGLERSHKSSKGGSSRDTKGSKDKNSRSDRKRSISESSR  
 SGKRSSRSERDRKSDRKDKRR

SEQ ID No:227

MLRLSERNMKVLLAAALIAGSVFFLLLPGPSAADEKKKGPKVTVKVYFDLRIGDEDVGRV  
 IFGLFGKTVPKTVDNFVALATGEKGFGYKNSKFHRVIKDFMIQGGDFTRGDGTGGKSIY



GERFPDENFKLKHYGPGWVSMANAGKDTNGSQFFITTVKTAWLDGKHVVFGKVLEGM  
EVVRKVESTKTDSRDKPLKDVIIADCGKIEVEKPFIAIAKE

SEQ ID No:228

MASCVGSRTLKDDVNYKMHFRMINEQQVEDITIDFFYRPHTITLLSFTIVSLMYFAFTRD  
DSVPEDNIWRGILSVIFFFLIISVLAFPNGPFTRPHPALWRMVFGLSVLYFLFLVLLFLNF  
EQVKSLMYWLDPNLRyatREADVMEYAVNCHVITWERIISHFDIFAFGHFWGWAMKAL  
LIRSYGLCWTISITWELTEFFMHLLPNFAECWWDQVILDILLCNGGGIWLGMVVCRFLE  
MRTYHWASFKDIHTTTGKIKRAVLQFTPASWTYVRWFDPKSSFQRVAGVYLFMIWQLT  
ELNTFFLKHFVVFQASHPLSWGRILFIGGITAPTvrQYYAYLTDTQCKRVGTQCWVFGVI  
GFLEAIVCIKFGQDLFSKTQILYVVLWLLCVAFTTFLCLYGMiWYAEHYGHREKTYSECE  
DGTYSPEISWHHRKGTkGSEDSPPKHAGNNESHSSRRRRNRHskSKVTNGVGKK

SEQ ID No:229

MAEAKTHWLGAALSLIPLIFLISGAEEASFQRNQLLQKEPDLRLENVQKFPSPeMIRALE  
YIENLRQQAHKEESSPDYNPYQGVSVPLQQKENGDESHLPERDSLSEEDWMRIILEAL  
RQAENEPQSAPKENKPYALNSEKNFPMDSDDYETQQWPERKLKHMqFPPMYEENS  
RDNPFKRTNEIVEEQYTPQSLATLESVFQELGKLTGPNNQKRERMDEEQKLYTDDeddi  
YKANNIAYEDVVGGEDWNPVEEKIESQTQEEVRDSKENIGKNEQINDEMKRSGQLGIQ  
EEDLRKESKDQLSDDVSKVIAYLKRLVNAAGSGRLQNGQNGERATRLFEKPLDSQSIYQ  
LIEISRNlQIPPEDLIEMLKTGEKPNGSVEPERELDLPVDLDDISEADLDHPDLFQNRMLS  
KSGYPKTPGRAGTEALPDGLSVEDILNLLGMESAANQKTSYFPNPYNQEKVLPRLPYG  
AGRSRSNQLPKAAWIPHVENRQMAYENLNDKDQELGEYLARMLVKYPEIINSNQVKRV  
PGQGSSedDLQEEEQIEQAIKEHLNQGSSQETDKLAPVSKRFPVGPpKNDDTPNRQY  
WDEDLLMKVLEYLNQEKAekGREHIAKRAMENM

SEQ ID No:230

MAVVKNKCLMKGGKKGvKKKIIDPFSKKDQKYWKDLVTRTQGTQIASDGLKGLVFEVSL  
ADVQNDEVAFRKLKLITEDVQGKNCLTNFYGMGLSCDKICSMFENCSTMIEAHVDVKTt  
DDNIGKDVEKACQFILSMMSLEKGREFQHHFWPLKKAATIRMSSPHVTISRDSKEEGN  
KAASSHYSRGGAKYEGEAVKRSLVESYTHPNskETERRENIDTVLNWFTKEEFDFVTLY  
YREPDNMGHRFRPEAENRKLMIQQINRTIGPWDDHREEETQCQQDPLSNYIKFRDCVK  
FDIVGYGGFGMPLTKLGQEEALYQALKNVHPDLHVYKKEFPEDFHLAKHDQVLPIMMYA  
NCGYSINGRIIMCFNKGSHGFDNVLMdiKTIFRDfGPDFKRNRlaEPFNSIHYPFVSPGS

HPQTHNGSLAVTQEMLMSSYDQQPGGRRGERRGPGQSRESRGRRDGSPCRSPRHA  
 RHGEITQRFANTFYCVFNVPVNAPLRFLSLPSTQSLEAKLTDSSDSELLRDILQKTVKHP  
 VCVTHPPSVKYARCFELSELIKKEAVHTEPLDELYEVLVETLMAKESTQGHWSYLLDCP  
 RAWQWCWPHSPGHLQDVPPPGIHLQRLSQPGPQTAPRECPSQWPLIRGRHHCQLSP  
 RVTVAQLDWDIAMVHQLSAIQPDVVIAADVLYCPEAIVLLVGVLLRLAACREHQRAPEVY  
 VAFTVRNPETCQLFTTELQARIRWEVEPRHDQKLPYEEHLEMAMNLTL

SEQ ID No:231

MSSQPAGNQTSPGATEDYSYGSWYIDEPQGGEELQPEGEVPSCHTSIPPGLYHACLA  
 SLSILVLLLLLAMLVRRRQLWPDCVRGRPGLPSPVDFLAGDRPRAVPAAVFMVLLSSLCL  
 LLPDEDALPFLTASAPSQDGKTEAPRGAWKILGLFYAAALYYPLAACATAGHTAAHLLG  
 STLSWAHLGVQVWQRAECPQVPKIYKYSSLLASLPLLLGLGFLSLWYPVQLVRSFSRRT  
 GAGSKGLQSSYSEEYLRNLLCRKKLGSSYHTSKHGFLSWARVCLRHCIYTPQPGFHLP  
 LKLVLSATLTGTAIYQVALLLLVGVVPTIQKVRAGVTDDVSYLLASFGIVLSEDKQEVVELV  
 KHHLWALEVCYISALVLSCLLTLFLVLMRSLVTHRTNLRALHRGAALDLSPLHRSPHPSRQ  
 AIFCWMSFSAYQTAFICLGLLVQQIIFFLGTTALAFLVLMPVLHGRNLLLFRSLESSWPFW  
 LTLALAVILQNMAAHWVFLETHDGHPLTNRRVLYAATFLLFPLNVLVGAMVATWRVLL  
 SALYNAIHLGQMDLSLLPPRAATLDPGYTYRNFLKIEVSQSHPAMTAFCSLLLQAQSL  
 PRTMAAPQDSLPGEEDEGMQLLQTKDSMAKGARPGASRGRARWGLAYTLLHNPTL  
 QVFRKTALLGANGAQP

SEQ ID No:232

GTRGPPGSPPPPHVRGMPGCPGCGMAGPRLLFLTALALELLGRAGGSQPALRSR  
 GTATACRLDNKESESWGALLSGERLDTWICSLLGSLMVGLSGVFPLLVIPLEMGTMRLS  
 EAGAWRLKQLLSFALGGLLGNVFLHLLPEAWAYTCSASPGGEGQSLQQQQQLGLWVI  
 AGILTFLALEKMFLDSKEEGTSQAPNKDPTAAAAALNGGHCLAQPAAEPLGAVVRSIK  
 VSGYLNLLANTIDNFTHGLAVAASFLVSKKIGLLTTMAILLHEIPHEVGDFAILLRAGFDRW  
 SAAKLQLSTALGGLLGAGFAICTQSPKGVVGCSPAAEETAAWVLPFTSGGFLYIALVNVL  
 PDLLEEDPWRSLLQQLLLLCAGIVVMVLFSLFVD

SEQ ID No:233

MAERRRHKKRIQEVGEPSSKEEKAVAKYLRFNCPKSTNMMGHRVDYFIASKAVDCLLD  
 SKWAKAKKGEEALFTTRESVVDYCNRLKKQFFHRALKVMKMKYDKDIKKEKDKGKAE  
 SGKEEDKKS KENIKDEKTKKEKEKKDGEKEESKKEETPGTPKKKETKKKFKLEPHDD

QVFLDGNEVYVWIYDPVHFKTFVMGLILVIAVIAATLFPLWPAEMRVGVYYLSVGAGCFV  
 ASILLAVARCILFLIWLITGGRHHFWFLPNLTADVGFIDSFRPLYTHEYKGPKADLKKDE  
 KSETKKQKQSDSEEKSDSEKKEDEEGKVGPNGHGTGSGGERHSDTDSDRREDDRS  
 QHSSGNGNDFEMITKEELEQQTDGDCCEEDDEEEENDGETPKSSHEKS

SEQ ID No:234

MAAEGWIWRWGWGRRCLGRPGLLGPGPGPTTPLFLLLLLGSVTADITDGNSEHLKRE  
 HSLIKPYQGVGSSSMPLWDFQGSTMLTSQYVRLTPDERSKEGSIWNHQPCFLKDWEM  
 HVHFKVHGTGKKNLHGDGIALWYTRDRLVPGPVFGSKDNFHLAIFLDITYPNDEETTER  
 VFPYISVMVNNGSLSYDHSKDGRWTELAGCTADFRNRDHDFTLAVRYSRGRLTVMIDL  
 EDKNEWKNCIDITGVRLPTGYFYGASAGTGDLSNDHDIISMKLFQLMVEHTPDEESIDW  
 TKIEPSVNLKSPKDNVDDPTGNFRSGPLTGWRVFLLLLALLGIVVCAVVGAVVFQKR  
 QERNKRFY

SEQ ID No:235

MDSNTAPLGPSCPQPPAPQPQARSRLNATASLEQERSERPRAPGPQAGPGPGVRD  
 AAAPAEPPAQHTRSRRERADGTGPTKGDMEIPFEEVLERAKAGDPKAQTEVGKHYLQLA  
 GDTDEELNSCTAVDWLVLAQKQGRREAVKLLRRCLADRRGITSENEREVRQLSSETDL  
 ERAVRKAALVMYWKLNPKKKKQVAVAELENVGVNEHDGGAQPGVPKSLQKQRR  
 MLERLVSSSESKNYIALDDFVEITKKYAKGVIPSSLFLQDDEDDDELAKSPEDLPLRLKV  
 VKYPLHAIMEIKEYLIDMASRAGMHWLSTIIPTHHINALIFFFIISNLTIDFFAFFIPLVIFYLSF  
 ISMVICTLKVFQDSKAWENFRTLTDLLLRFEPNLDVEQAEVNFVGNHLEPYAHFLLSVFF  
 VIFSFPISKDCIPCSELAVITGFFTVTSLSLSTHAEPYTRRALATEVTAGLLSLLPSMPL  
 NWPYLKVLGQTFITVPVGHVVLNVSVPCLLYVYLLYLFFRMAQLRNFKGTYCYLVPYLV  
 CFMWCELSVVILLESTGLGLLRASIGYFLFLFALPILVAGLALVGVLQFARWFTSLELTkia  
 VTVAVCSVPLLLRWWTkasfsvvgmvksltrssmvklilvwltailvfcwfyvyrsegm  
 KVYNSTLTWQQYGALCGPRAWKETNMARTQILCSHLEGHRVTWTGRFKYVRVTDIDN  
 SAESAINMLPFFIGDWMRCLYGEAYPACSPGNTSTAEELCRLKLLAKHPCHIKKFDry  
 KFEITVGMPFSSGADGSRsreeddvTKDIVLRASSEFKSVLLSLRQGSLEFSTILEGRlg  
 SKWPVFELKAISCLNCMAQLSPTRRHVKIEHDWRSTVHGAVKFAFDFFFFFPFLSAA

SEQ ID No:236

MNNQKQKQPTLSGQRFKTRKRDEKERFDPTQFQDCIIQGLTETGTDLEAVAKFLDASG  
 AKLDYRRYAETLFDILVAGGMLAPGGTLADDMMRTDVCVFAAQEDLETMQAFAQVFNK

LIRRYKYLEKGFEDVKKLLLFLKGFSESERNKLAMLTGVLLANGTLNASILNSLYNENLV  
KEGVSAFAVKLFKSWINEKDINAVAASLRKVSMDNRLMELFPANKQSVEHFTKYFTEA  
GLKELSEYVRNQQTIGARKELQKELQEQMSRGDPFKDIILYVKEEMKKNNIPEPVVIGIV  
WSSVMSTVEWNNKEELVAEQAIKHLKQYSPLLAFTTQGGQSELTLLLKIQEYCYDNIHF  
MKAQKIVVLFYKAEVLSEEPILKWKYKDAHVAKGKSVFLEQMKKFVEWLKNAEEEESESE  
AEEGD

SEQ ID No:237

MENHKSNNKENITIVDISRKINQLPEAERNLLENGSVYVGLNAALCGLIANSLFRRILNVT  
KARIAAGLPMAGIPFLTTLTYRCFVSFPLNTGDLDCETCTITRSGLTGLVIGGLYPVFLAI  
PVNGGLAARYQSALLPHKGNILSYWIRTSKPVFRKMLFPILLQTMFSAYLGSEQYKLLIK  
ALQLSEPGKEIH

SEQ ID No:238

MGDILAHESSELLGLVKEYLDFAEFEDTLKTFSKECKIKGKPLCKTVGGSFRDSKSLTIQK  
DLVAAFDNGDQKVFFDLWEEHISSSIRDGDSFAQKLEFYLIHFAYLLKYSVGRPDKEE  
LDEKISYFKTYLETGGAALSQTTEFLPFYALPFVPMVHPSFKELFQDSWTPELKLE  
KFLALISKASNTPKLLTIYKENGQSNKEILQQLHQQLVEAERRSVTYLKRYNKIQADYHNL  
IGVTAELVDSLEATVSGKMITPEYLQSVCVRLFSNQMRQSLAHSVDFTRPGTASTMLRA  
SLAPVKLKDVPLLPOLDYEKLKDLILGSDRLKAFLLQALRWRLTTSHPGEQRETVLQAY  
ISNDLLDCYSHNQSVLQLLHSTSDVVRQYMARLINAFAELAEGRLYLAQNTKVLQMLE  
GRLKEEDKDIITRENVPGALQKFSRLRPLQTAMIQDGLIFWLVDVLKDPDCLSDYTLAYS  
VALLMNLCLRSTGKNMCAKVAGLVVKVLSDLLGHENHEIQPYVNGALYSILSVPSIREEA  
RAMGMEDILRCFIKEGNAEMIRQIEFIKQLNSEELPDGVLESDDDEDEDDEEDHDIMEA  
DLDKDELIQPQLGELSGEKLTTTEYLGIMTNTGKTRRKGLANVQWSGDEPLQRPVTPG  
GHRNGYPV

SEQ ID No:239

IATVIVITLVMLKKKQYTSIHGVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID No:240

MSAGSERGAAATPGGLPAPCASKVELRLSCRHLLDRDPLTKSDPSVALLQQAQGQWV  
QVGRTEVVRSSLHPVFSKVFTVDYYFEEVQRLRFVYDTHGPSGFSCQEDDFLGME  
CTLGQPAQKWLLQVVMRVSVDVLGPAGHCAKHFLCCTESSHLARTGPSFLLRYDDLCL

PWATAGAVRWWTCRGGHTQGWQIVAQKKVTRPLLLKFGRNAGKSTITVIAEDISGNNG  
YVELSFRARKLDDKDLFSKSDPFLELYRVNDDQGLQLVYRTEVVKNNLNPVWEAFKVS  
LSSLCSCETRPLKCLVWDYDSRGKHDFIGEFSTTFEEMQKAFFEGQAQWDCVNPKY  
KQKRRSYKNSGVVVLADLKFHRVYSFLDYIMGGCQIHFTVAIDFTASNGDPRNSCSLHYI  
NPYQPNEYLKALVSVGEICQDYDSDKRFSALGFGARIPPKYEVSDFAINFNPEDDECE  
GIQGVVEAYQNCLPRVQLYGPTNVAPIISKVARVAAAEEESTGKASQYYILLITDGVVTD  
MADTREAIVRASRLPMSIIIVGVGNADFTDMQVLDGDDGVLRSRGPALRDIVQFVPF  
RELKNASPAALAKCVLAEVPKQVVEYYSHRGLPPRSLGVPAGEASPGCTP

SEQ ID No:241

MAAQCVTKVALNVSCANLLDKDIGSKSDPLCVLFLNTSGQQWYEVERTERIKNCLNPQF  
SKTFIIDYYFEVVQKLKFGVYDIDNKTIELSDDDFLGECECTLGQIVSSKKLTRPLVMKTG  
RPAGKGSITISAEIKNRVVLFEMEARKLDNKDLFGKSDPYLEFHKQTSNGNWLMMVHR  
TEVVKNNLNPVWRPFKISLNSLCYGDMDKTIKVECYDYDNDGSHDLIGTFQTTMTKLKE  
ASRSSPVEFECINEKKRQKKKSYKNSGVISVKQCEITVECTFLDYIMGGCQLNFTVGVDF  
TGSNGDPRSPDSLHYISPNGVNEYLTALWSVGLVIQDYDADKMFPAFGFGAQIPPQWQ  
VSHEFPMNFPNSNPYCNGIQGIVEAYRSCLPQIKLYGPTNFSPIINHVARFAAAATQQQT  
ASQYFVLLIITDGVITDLDETRQAIVNASRLPMSIIIVGVGGADFSAMEFLDGDGGSLSRPL  
GEVAIRDIVQFVPFRQFQNPKEALAQCVLAEIPQQVVG YFNTYKLLPPKNPATKQQKQ

SEQ ID No:242

RHTRTHRDTRHTYTHAHTDAHTCTHMRDQTQMHTHTICRKKYALTNIQAAMGLSDPAA  
QPLLGNNGSANIKLVKNGENQLRKAAEQGQQDPNKNLSPTAVINITSEKLEGKEPHPQDS  
SSCEILPSQPRRTKSFLNYYADLETSAARELEQNRGNHHGTAEKKSQPVQGGQASTIING  
DLLLQKPNRPQSSPEDGQVATVSSSPETKKDHPKTGAKTDCALHRIQNLAPEDESSW  
TTLSQDSASPSPDETDIWSDHSFQTDPLPPGWKRVS DIAGTYWHIPTGTTQWERP  
VSIPADLQGSRKGSLSVTPSPTPENKQPWSDFAVLNGGKINS DIWKDLHAATVNPDP  
SLKEFEGATLRYASLKL RNAPHPDDDDSCSINS DPEAKCFAVRSLGWVEMAEEDLAPG  
KSSVAVNNCIRQLSYCKNDIRDTVGIWGEGKDMYLILENDMLSLVDPMDRSVWHSQPIV  
SIRVWGVGRDNGRD FAYVARDKDTRILKCHVFRCDTPAKAIATSLHEICSKIMAERKNAK  
ALACSSLQERANVNLDVPLQVDFPTPKTELVQKFHVQYLGMLPVDKPVGMDILNSAIEN  
LMTSSNKEDWLSVNMNVADATVTVISEKNEEEVLVECRVRFLSFMGVGKDVHTFAFIM  
DTGNQRFECVFWCEPNAGNVSEAVQAACMLRYQKCLVARPPSQKVRPPPPPADSV  
TRRVTTNVKRGVLSLIDTLKQKRPVTEMP

SEQ ID No:243

MSGFSPELIDYLEGKISFEEFERRREERKTREKKSLQEKGKLSAEENPDDSEVPSSSGI  
NSTKSQDKDVNEGETSDGVRKSVHKVFASMLGENEDDEEEEEEEEEEEEEETPEQP  
TAGDVFVLEMVLNRETKKMMKEKRPRSKLPRALRGLMGEANIRFARGEREEAILMCMEI  
IRQAPLAYEPFSTLAMIYEDQGDMEKSLQFELIAAHLNPSDTEEWVRLAEMSLEQDNIQ  
AIFCYTKALKYEPTNVRYLWERSSSLYEQMGDHKMMAMDGYRRILNLLSPSDGERFMQLA  
RDMAKSYEANDVTSAINIIDEAFSKHQGLVSMEDVNIAAELYISNKQYDKALEIITDFSGI  
VLEKKTSEEGTSEENKAPENVCTIPDGVPIDITVKLMVCLVHLNILEPLNPLLTTLVEQN  
PEDMGDLYLDVAEAFLDVGEYNSALPLLSALVCSERYNLAVVWLRHAECLKALGYMER  
AAESYGKVVLDAPLHLDARISLSTLQQQLGQPEKALEALEPMPYDPDTLAQDANAAQQEL  
KLLHHRSTLLFSQGKMYGYVDTLTMLAMLLKVAMNRAQVCLISSSKSGERHLYLIKVSR  
DKISDSNDQESANCDAKAIFAVLTSVLTKDDWWNLLLKAIYSLCDLSRFQEAELLVDSSL  
EYYSFYDDRQKRKELEYFGLSAAILDKNFRKAYNYIRIMVMENVNKPQLWNIFNQVTMH  
SQDVRHHRFCLRLMLKNPENHALCVLNGHNAFVSGSFKHALGQYVQAFRTHPDEPLY  
SFCIGLTFIHMASQKYVLRHALIVQGFSLNRYLSLRGPCQESFYNLGRGLHQLGLIHL  
AIHYYQKALELPPLVVEGIELDQLDLRRDIAYNLSLIYQSSGNTGMAQTLLYTYCSI

SEQ ID No:244

MLRRVTVAAVCATRRKLCEAGRELAALWGIETRGRCEDSAAARPPILAMPGRNKAKS  
TCSCPDLQPNGQDLGENSRVARLGADESEEEGRRGSLSNAGDPEIVKSPSDPKQYRYI  
KLQNGLQALLISDLNMEGKTGNTTDDDEEEEEVEEEEEDDEDGSAEIEDDDEEGFDDE  
DEFDDEHDDDLDTEDNELEEELEERAERKKTTEKQSAAALCVGVGSFADPDDLPLGLAH  
FLEHMFVFMGSLKYPDENGFD AFLKKHGGSDNASTDCERTVFQFDVQRKYFKEALDRW  
AQFFIHPLMIRDAIDREVEAVDSEYQLARPSDANRKEMLFGSLARPGHPMGKFFWGNA  
ETLKHEPRKNNIDTHARLREFWMRYSSHYMTLVVQSKETLDTLEKWVTEIFSQIPNNG  
LPRPNFGHLTDPFDTPAFNKLYRVVPIRKIHALTITWALPPQQQHRYVKPLHYISWLVGH  
EGKGSILSFLRKKCWALALFGGNGETGFEQNSTYSVFSISITLTDEGYEHFYEVAYTVFQ  
YLKMLQKLGPEKRIFEEIRKIEDNEFHYQEQTDPVEYVENMCENMQLYPLQDILTGDQLL  
FEYKPEVIGEALNQLVPQKANLVLLSGANEGKCDLKEKWFGTQYSIEDIENSWGELWNS  
NFELNPDLHLPAENKYIATDFTLKAFDCPETEYPVKIVNTPQGCLWYKKDNKFKIPKAYIR  
FHLISPLIQKSAANVVLFDIFVNILTHNLAEPAYEADVAQLEYKLVAGEHGLIIRVKGFNHK  
LPLLFQLIIDYLAEFNSTPAVFTMITEQLKKTYNILIKPETLAKDVRLILEYARWSMIDKY  
QALMDGLSLESLLSFVKEFKSQLFVEGLVQGNVTSTESMDFLKYVVDKLNFKPLEQEMP

VQFQVVELPSGHHLCKVKALNKG DANSEVT VYYQSGTRSLREY TLMELLVMHMEEP CF  
DFLRTKQTLGYHVYPTCRNTSGILGFSVTVGTQATKYNSEVVDKKIEEFLSSFE EK IENL  
TEEAFNTQVTALIKLKECEDTHLGEEVDRNWNEVVTQQYLFDR LAHEIEALKSFSKSDLV  
NWFKAHRGPGSKMLSVHAVGYGKYELEEDGTPSSEDSNSSCEVMQLTYLPTSPLLAS  
VSSPLLISGLSQQHSTFSPTIK

SEQ ID No:245

MAEVGEIIEGCRLPVLRRNQDNEDEWPLAEILSVKDISGRKLFYVHYIDFNKRLDEWVTH  
ERLDLKKIQFPKKEAKTPTKNGLPGSRPGSPEREVPASAQASGKTLPIPVQITLRFNLPK  
EREAIPGGEPDQPLSSSSCLQPNHRSTKRKVEVVS PATVPSETAPASVFPQNGAARR  
AVAAQPGRKRKSNCLGTDEDSQDSSDGIPSAPRMTGSLVSDRSHDDIVTRMKNIECIEL  
GRHRLKPWYFSPYPQELTTLPVLYLCEFCCLKYGRSLKCLQRHLTKCDLRHPPGNEIYRK  
GTISFFEIDGRKNKSYSQNLCLLAKCFLDHKTLYYDTPFLFYVMTEYDCKGFHIVGYFS  
KEKESTEDYNVACILTLPYQRRGYRKLLIEFSYELSKVEGKTGTPEKPLSDLGLLSYRS  
YWSQTILEILMGLKSESGERPQITINEISEITSIKKEDVISTLQYLNLYYKQYILTSEDI  
VDGHERAMLKRLLRIDSKCLHFTPKDWSKRGKW

SEQ ID No:246

MASGRDERPPWRLGRLLLLMCLLLLGSSARAAHIKKAEATTTTTTSAGAEAAEGQFDRY  
YHEEELESALREAAAAGLPGLARLFSIGRSVEGRPLWVLRLTAGLGLIPEGDAGPDAA  
GPDAAGPLLPGRPQVKLVGNMHGDETVSRQVLIYLARELAAGYRRGDPRLVRLNNTD  
VYLLPSLNPDGFERAREGDCGFGDGGPSGASGRDNSRGRDLNRSFPDQFSTGEPPAL  
DEVPEVRALIEWIRRNKFVLSGNLHGGSVVASYPFDD SPEHKATGIYSKTSDDDEVFKYL  
AKAYASNHPIMKTGEPHCPGDEDETFKDGITNGAHWYDVEGGMQDYNVWANCEFIT  
LELSCCKYPPASQLRQEWENNRESLITLIEKVHIGVKGFVKDSITGSGLENATISVAGINH  
NITTGRFGDFYRLLVPGTYNLT VVLTGYMPLTVTNVVVKEGPATEVDFSLRPTVTSVIPD  
TTEAVSTASTVAIPNILSGTSSSYQPIQPKDFHHHHFPDMEIFLRRFANEYPNITRLYSLG  
KSVESRELYVMEISDNPGVHEPGEPEFKYIGNMHGNEVVGRELLNLIEYLCKNFGTDP  
EVTDLVHNTRIHLMPSPMNP DGYEKSQEGDSISVIGRNNSNNFDLNRNFPDQFVQITDPT  
QPETIAVMSWMKSYPFVLSANLHGGSLVVNYPFDDDEQGLATYSKSPDDAVFQQIALS  
YSKENSQMFQGRPCKNMYPNEYFPHGITNGASWYNVPGGMQDWNYLQTNCFEVTIEL  
GCVKYPLEKELPNFWEQNRRSLIQFMKQVHQGVRGFVL DATDGRGILNATISVAEINHP  
VTTYKTGDYWRLLVPGTYKITASARGYNPVTKNVTVKSEGAIQVNFTLVRSSSTD SNNES  
KKGKGASSSTNDASVPTTKEFETLIKDL SAENGLESMLRSSSNLALALYRYHSYKDLSE

FLRGLVMNYPHITNLNLGQSTEYRHIWSLEISNKNPVSEPEEPKIRFVAGIHGNAPVGT  
 ELLLALAEFLCLNYKKNPAVTQLVDRTRIVIVPSLNPDGRERAQEKDCTSKIGQTNARGK  
 DLDTDFTNNASQPETKAIENLIQKQDFSLSVALDGGSMMLVTYPYDKPVQTVENKETLKH  
 LASLYANNHPSMHMGQPSCPNKSDENIPGGVMRGAEWHSGLGSMKDYSVTYGHCP  
 TVYTSCCYFPSAARLP  
 SLWADNKRSLLSMLVEVHKG  
 VHG  
 FVKDKTGKPI  
 SKAVIVLNEGI  
 KVQTKEGGYFHVLLAPGVHNI  
 AIADGYQQQHSQV  
 FVHHDAASSV  
 VVIVFDTDN  
 RIFGLPR  
 ELVVTVSGATMSALILTACI  
 W  
 CICSISNRHKDGFHRLRQHHDEYE  
 DEIRMMSTGSKKS  
 LLSHEFQDETDT  
 EETLYSSKH

SEQ ID No:247

MASLYQRFTGKINTSRSPAPPEASHLLGGQGPEEDGGAGAKPLGPRAQAAAPRERG  
 GGGGGAGGRPRFQYQGRSDGDEEDELVGSNPPQRNWKGIAIALLVILVICSLIVTSVILL  
 TPAEDNSLSQKKKVTVEDLFSDFKIHDPEAKWISDTEFIYREQKGT  
 VRLWNVETNTST  
 VLIEGKKIESLRAIRYEISPDREYALFSYNVEPIYQHSYTGYYVLSKIPHGDPQSLDPPEVS  
 NAKLQYAGWGPKGQQLIFENNIYYCAHV  
 GKQAIRVVSTGKEGVIYNGLSDWLYEEEEIL  
 KTHIAHWWSPDGT  
 RLAYAAINDSRVPIMELPTYTGS  
 IYPTVKPYHYPKAGSENPSISLHVI  
 GLNGPTHDLEMMPPDDPRMREYYITMV  
 KWATSTKVAVTWLNRAQNVSILTLCDATTGV  
 CTKKHEDESEAWLHRQNEEPVFSKDGRKFF  
 FIRAI  
 PQGGRGKFYHITVSSSQPNSSND  
 NIQSITSGDWDVT  
 KILAYDEKGNKIYFLSTEDLPRRRQLYSAN  
 TEGNFRQCLSCDLVEN  
 CTYFSASF  
 SHSMDFFLLKCEGPGVPMVTVHNTT  
 DKKKMFDLETNEHVKKAINDRQMPK  
 VEYRDIEIDDYNLPMQILKPATFTDTTHY  
 PLLLVVDGTPGSQSVAEKFEVSWETVMVSSH  
 GAVVVKCDGRGSGFQGTKLLHEVRRRLGL  
 LEEKDQMEAVRTMLKEQYIDRTRVAVFG  
 KDYGGYLSTYILPAKGENQGQTFTCGSAL  
 SPITDFKLYASAFSERYLGLHGLDNRAYEM  
 TKVAHRVSALEEQQFLIIHPTADEKIH  
 FQHTAELITQLIRGKANYS  
 LQIYPDESHYFTSSSL  
 KQHLYRSIINFFVECFRIQDKLPTVTAKED  
 EEEEE

SEQ ID No:248

IQTSGACRARS  
 GGGGRDRGCTGRGCGADARAGAAMVKISFQPAVAGIKGDKADKASAS  
 APAPASATEILLTPAREEQPPQHR  
 SKRGGSVGGVCYLSMGMVVLLMGLVFASVYIYRYF  
 FLAQLARDNFFRCGVLYEDSLSSQV  
 RTQMELEEDVKIYLDENYERINVPVPQFGGGDPA  
 DIIHDFQRGLTAYHDISLDKCYVIELNTTIVLPP  
 RNFWELLMNVKRGTYLPQTYIIQEEMVV  
 TEHVSDKEALGSFIYHLCNGKDTYRLRRRATRRR  
 RINKRGAKNCNAIRHFENTFVVETLIC  
 GVV



SEQ ID No:249

MVKVTFNSALAQKEAKKDEPKSGEEALIIPPDAAVAVDCKDPDDVVPVGQRRRAWCWCM  
CFGLAFMLAGVILGGAYLYKYFALQPDDVYYCGIKYIKDDVILNEPSADAPAALYQTIEEN  
IKIFEEEEVEFISVPVPEFADSDPANIVHDFNKKLTAYLDLNLDKCYVIPLNTSIVMPPRNL  
LELLINIKAGTYLPQSYLIHEHMTDRIENIDHLGFFIYRLCHDKETYKLQRRETIKGIQKR  
EASNCFAIRHFENKFAVETLICS

**CLAIMS**

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
2. A protein complex comprising a first protein selected from the proteins listed in table 1, fourth column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm

DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

3. A protein complex comprising all proteins selected from the proteins in table 1, third column of a given complex or at least one protein being a homologue thereof, or a variant thereof or functionally active fragment or functionally active derivative of said protein, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions;  
wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or at least one protein being a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, except at least one protein of the proteins listed in table 5, third column, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, with the proviso that the complex comprises at least one protein selected from table 1, fifth column of a given complex.

5. The complex of any of Claim 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of Claim 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of Claim 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of Claim 1 - 7 that is involved in at least one biochemical activity as stated in table 3.
9. A process for preparing a complex of any of Claim 1 - 8 and optionally the components thereof comprising the following steps:  
expressing a protein of the complex, preferably a tagged protein, in a target cell, or a tissue or an organ, isolating the protein complex which is attached to the protein, preferably the tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to Claim 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of Claim 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of a protein complex obtainable by a process according to any of Claim 9 - 11.
13. Protein selected from the group of proteins in table 1, sixth column of a given complex or a homologue or a variant of thereof, or a functionally active fragment or a

functionally active derivative of said protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

14. Nucleic acid encoding a protein according to Claim 13.
15. Construct, preferably a vector construct, comprising
  - (a) a nucleic acid according to Claim 14 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
  - (b) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to Claim 1 (a) and at least one of said proteins, being selected from the second group of proteins according to Claim 1 (b) or
  - (c) at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, said proteins being selected from the proteins of complex (II) according to Claim 1.
16. Host cell, containing a vector comprising at least one nucleic acid of Claim 14 and /or a construct of Claim 15 or containing several vectors each comprising at least one nucleic acid encoding at least one protein selected from the first group of proteins according to Claim 1 (a) and at least one nucleic acid encoding at least one protein selected from the second group of proteins according to Claim 1 (b).
17. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of

Claim 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed and an antibody or a fragment of said antibody containing the binding domain thereof which binds to any of the proteins of the group of proteins according to Claim 13.

18. A kit comprising in one or more containers:

- (a) the complex of any of Claim 1 – 8 and/or the proteins of Claim 13 and/or
- (b) an antibody according to Claim 17 and/or
- (c) a nucleic acid encoding a protein of the complex of any of Claim 1 – 8 and/or a protein of Claim 13 and/or
- (d) cells expressing the complex of any of Claim 1 – 8 and/or a protein of Claim 13 and, optionally,
- (e) further components such as reagents, buffers and working instructions.

19. The kit according to Claim 18 for processing a substrate of a complex of any one of Claim 1 - 8.

20. The kit according to Claim 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as those as stated in column 2, table 4 of a given complex.

21. Array, preferably a microarray, in which at least a complex according to any of Claim 1 - 8 and/or at least one protein according to Claim 13 and/or at least one antibody according to Claim 17 is attached to a solid carrier.

22. A process for modifying a substrate of a complex of any one of Claim 1 - 8 comprising the step of bringing into contact a complex of any of Claim 1 - 8 with said substrate, such that said substrate is modified.

23. A pharmaceutical composition comprising the protein complex of any of Claim 1 - 8 and/or a protein according to Claim 13.

24. A pharmaceutical composition according to Claim 23 for the treatment of diseases and disorders, preferentially for diseases or disorders such as those as stated in column 2, table 4 of a given complex.
25. A method for screening for a molecule that binds to a complex of any one of Claim 1 - 8 and/or a protein of Claim 13, comprising the following steps:
- (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.
26. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of a complex of any one of Claim 1 - 8 comprising the steps of:
- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.
27. The method of Claim 26, wherein the amount of said complex is determined.
28. The method of Claim 26, wherein the activity of said complex is determined.

29. The method of Claim 28, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
30. The method of Claim 26, wherein the amount of the individual protein components of said complex is determined.
31. The method of Claim 30, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
32. The method of any of Claim 26 - 31, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as those as stated in column 2, table 4 of a given complex.
33. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of Claim 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as those as stated in column 2, table 4 of a given complex.
34. A method for the production of a pharmaceutical composition comprising carrying out the method of Claim 26 - 31 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.



35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the Claim 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene regulated by the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in a corresponding sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.
36. The method of Claim 35, wherein the amount of said complex is determined.
37. The method of Claim 35, wherein the activity of said complex is determined.
38. The method of Claim 37, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
39. The method of Claim 35, wherein the amount of the individual protein components of said complex is determined.
40. The method of Claim 39, wherein said determining step comprises determining whether any of the proteins according to Claim 13 is present in the complex.
41. The complex of any one of Claim 1 - 8, or a protein of Claim 13 or an antibody or fragment thereof of Claim 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as those as stated in column 2, table 4 of a given complex.

42. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of Claim 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity of, or protein composition of, said complex.
43. The method according to Claim 42, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
44. The method according to Claim 42, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
45. Complex of Claim 1 - 8 and/or a protein as listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target, in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as a neurodegenerative disease such as those as stated in column 2, table 4 of a given complex.